

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

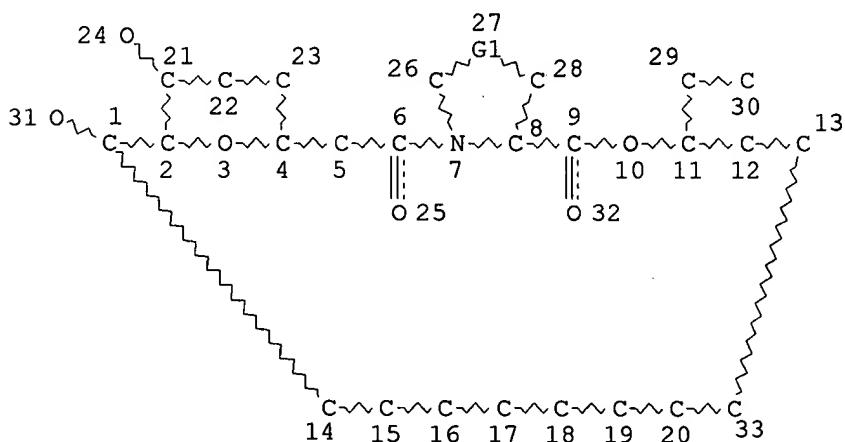
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FILE COVERS 1907 - 26 Feb 2003 VOL 138 ISS 9
 FILE LAST UPDATED: 25 Feb 2003 (20030225/ED)

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NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

MLEVEL IS CLASS AT 21 22 23

DEFAULT ECLEVEL IS LIMITED

ECOUNT IS UNLIMITED AT 21 22 23

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

L9 3512 SEA FILE=REGISTRY SSS FUL L7

L10 3995 SEA FILE=HCAPLUS L9

L12 27 SEA FILE=HCAPLUS L10 (L) (EYE? OR OPHTHAL? OR OCUL?)

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L12 ANSWER 1 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2003:77534 HCPLUS
 TITLE: Compositions and methods for enhancing drug delivery across and into ocular tissues
 INVENTOR(S): Rothbard, Jonathan B.; Wender, Paul A.; McGrane, P.
 Leo; Sista, Lalitha V. S.; Kirschberg, Thorsten A.
 PATENT ASSIGNEE(S): Cellgate, Inc., A Delaware Corporation, USA
 SOURCE: U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 792,480.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-------------------|----------|
| US 2003022831 | A1 | 20030130 | US 2002-83960 | 20020225 |
| US 2002127198 | A1 | 20020912 | US 2001-792480 | 20010223 |
| PRIORITY APPLN. INFO.: | | | US 1999-150510P P | 19990824 |
| | | | US 2000-648400 A2 | 20000824 |
| | | | US 2001-792480 A2 | 20010223 |

AB This invention provides compns. and methods for enhancing delivery of drugs and other agents across epithelial tissues, including into and across ocular tissues and the like. The compns. and methods are also useful for delivery across endothelial tissues, including the blood brain barrier. The compns. and methods employ a delivery-enhancing transporter that has sufficient guanidino or amidino side chain moieties to enhance delivery of a compd. conjugated to the reagent across one or more layers of the tissue, compared to the non-conjugated compd. The delivery-enhancing polymers include, for example, polyarginine mols. that are preferably between about 6 and 25 residues in length.

IT 104987-11-3, FK506
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (delivery-enhancing transporters for drug delivery across and into ocular tissues)
 IT 491875-85-5P 491875-86-6P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (delivery-enhancing transporters for drug delivery across and into ocular tissues)
 IT 491875-78-6P 491875-79-7P 491875-80-0P
 491875-81-1P 491875-82-2P 491875-83-3P
 491875-84-4P
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (delivery-enhancing transporters for drug delivery across and into ocular tissues)

L12 ANSWER 2 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2003:58810 HCPLUS
 DOCUMENT NUMBER: 138:83428
 TITLE: Tacrolimus formulations for the treatment of ocular disease
 INVENTOR(S): Peyman, Gholam A.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 6 pp., Cont.-in-part of U.S. Pat. Appl. 2002 13,340.

CODEN: USXXCO

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2003018044 | A1 | 20030123 | US 2002-247220 | 20020919 |
| US 2002013340 | A1 | 20020131 | US 2000-507076 | 20000218 |
| US 6489335 | B2 | 20021203 | | |

PRIORITY APPLN. INFO.: US 2000-507076 A2 20000218

AB A formulation to treat ocular disease, e.g. dry eye disease, as well as other diseases, is disclosed. Tacrolimus is administered intraocularly, e.g. topically or by injection. For topical administration, an amt. of about 1 ng to 10 .mu.g may be formulated in an aq. based cream that may be applied at bedtime or throughout the day. For injection, a dose of about 20-1000 .mu.g/mL is used. Tacrolimus may also be administered in milligram quantities as a surgical implant contained in a diffusible walled reservoir sutured to the wall of the sclera, or may be contained within an inert carrier such as microspheres or liposomes to provide a slow-release drug delivery system.

IT 104987-11-3, Tacrolimus

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (tacrolimus formulations for treatment of **ocular** disease)

L12 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:909458 HCAPLUS
 DOCUMENT NUMBER: 138:11234
 TITLE: Studies on the effects of the immunosuppressant FK-506 on the high-risk corneal graft rejection
 AUTHOR(S): Wang, Minhua; Lin, Yuesheng; Chen, Jiaqi; Liu, Yongming; Xie, Hanping; Ye, Chengtian
 CORPORATE SOURCE: Zhongshan Ophthalmic Center, Sun Yat-sen University, Canton, 510060, Peop. Rep. China
 SOURCE: Eye Science (2002), 18(3), 160-164
 CODEN: YAXUE3; ISSN: 1000-4432
 PUBLISHER: Zhongshan Ophthalmic Center
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB To evaluate the clin. efficacy of FK-506 on suppressing high-risk cornea transplantation rejection. In a randomized controlled clin. trial, 56 eyes of 56 patients with high-risk keratoplasty (including total corneal transplantation TCT, total corneal transplantation with circular lamellar sclera CST, vascularization corneal transplantation and corneal retransplantation) were divided into the exptl. group and the control group (each with 28 eyes). The exptl. group was treated by FK-506 eyedrops (0.5 mg/mL) and TobraDex eyedrops, compared with the control group that was treated by 1% CsA eyedrops and TobraDex eyedrops. In the av. 8.1-mo follow-up period, the visual acuity, graft transparent duration and Rejection Index (RI) of grafts were obsd. In the follow-up period, the graft rejection rate of the exptl. and the control group was 63.6% and 95.2% resp. (X2 = 4.72, P<0.05) with significant difference. The local application of FK-506 suppressed effectively the graft rejection of corneal transplantation of the patients at high risk.

IT 104987-11-3, FK-506

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (effects of immunosuppressant FK-506 and TobraDex **eyedrops** vs. CsA (Sandimmune) and TobraDex **eyedrops** on high-risk

corneal graft rejection in humans)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:832614 HCAPLUS
 DOCUMENT NUMBER: 137:329460
 TITLE: Macrocylic agent for topical ophthalmic treatment of ocular inflammatory diseases
 INVENTOR(S): Ueno, Ryuji
 PATENT ASSIGNEE(S): Sucampo A.-G., Switz.
 SOURCE: PCT Int. Appl., 39 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2002085359 | A1 | 20021031 | WO 2002-JP3664 | 20020412 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2002187998 | A1 | 20021212 | US 2002-120515 | 20020412 |

PRIORITY APPLN. INFO.: US 2001-283169P P 20010412

OTHER SOURCE(S): MARPAT 137:329460

AB The present invention provides an agent for topical ophthalmic treatment of a human for ocular inflammatory diseases, contg. a tricyclo compd. such as FK506 as the active ingredient in the concn. of 0.01% - 0.1%. The present agent for topical ophthalmic treatment continuously shows superior ocular anti-inflammatory effects by topically administering it in a low dose to the eye of the human having the ocular inflammatory diseases. The present agent is effective for symptoms caused by the ocular inflammatory diseases such as itching, flare, edema, ulcer, etc. The present agent is also effective for a subject in whom conventional anti-inflammatory agents show no improving effect (e.g., steroid and cyclosporins). The present agent is also effective for a subject for whom other anti-inflammatory agents cannot be used (e.g., steroid contraindication). Decreases in itching in patients were greater in exptl. groups instilled with 0.01, 0.06, and 0.1% FK506 eyedrops than in the control groups instilled with placebo.

IT 104987-11-3, Fk506

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (macrocylic agent for topical ophthalmic treatment of ocular inflammatory diseases)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:428756 HCAPLUS
 DOCUMENT NUMBER: 137:10999
 TITLE: Methods for reducing or preventing transplant rejection in the eye and intraocular implants for use

therefor
 INVENTOR(S): Wong, Vernon G.
 PATENT ASSIGNEE(S): Oculex Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 33 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2002043785 | A2 | 20020606 | WO 2001-US44481 | 20011128 |
| WO 2002043785 | A3 | 20021121 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002036495 | A5 | 20020611 | AU 2002-36495 | 20011128 |
| US 2002182185 | A1 | 20021205 | US 2001-997094 | 20011128 |
| PRIORITY APPLN. INFO.: US 2000-250023P P 20001129 US 2001-298253P P 20010612 WO 2001-US44481 W 20011128 | | | | |

AB Methods for reducing or preventing transplant rejection in the eye of an individual are described, comprising: (a) performing an ocular transplant procedure; and (b) implanting in the eye a bioerodible drug delivery system comprising an immunosuppressive agent and a bioerodible polymer. Sustained-release intraocular implant contg. HPMC 15, PLGA 35, and dexamethasone 50% were prep'd. The implants were implanted in the anterior chamber of the rat eyes at the end of cornea transplants surgery. Rats did not show any sign of rejection and the corneas stayed clear in all eyes. After 8 wk the graft survival was 100%.
 IT 104987-11-3, Tacrolimus
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (methods for reducing or preventing transplant rejection in eye and intraocular implants for use therefor)

L12 ANSWER 6 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:113132 HCPLUS
 DOCUMENT NUMBER: 136:156478
 TITLE: Topical compositions containing tacrolimus for treatment of immunological disease at front and surface of eyes
 INVENTOR(S): Chen, Jia-qi; Liu, Yong-min
 PATENT ASSIGNEE(S): Zhongshan University of Medical Science, Zhongshan Ophthalmology Center, Peop. Rep. China
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------|------|------|-----------------|------|
|------------|------|------|-----------------|------|

| | | | | |
|---------------|----|----------|----------------|----------|
| JP 2002047186 | A2 | 20020212 | JP 2001-82456 | 20010322 |
| CN 1333018 | A | 20020130 | CN 2000-117235 | 20000707 |
| US 2002173516 | A1 | 20021121 | US 2001-888342 | 20010622 |

PRIORITY APPLN. INFO.: CN 2000-117235 A 20000707

AB The invention relates to a topical compns. contg. tacrolimus hydrate or tacrolimus anhydride as an active ingredient for treatment of immunol. disease at front and surface of eyes, esp. in a form of an eye drop or an ophthalmic paste. An eye drop compn. contg. tacrolimus (FK506) 0.05, polyethylene hydrogenated castor oil 1, thickener 0.3, NaCl 0.75, antibacterial agent 0.002, and water q.s. to 100 % was formulated.

IT 104987-11-3, Tacrolimus 109581-93-3, Tacrolimus hydrate

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical compns. contg. tacrolimus for treatment of immunol. disease at front and surface of eyes)

L12 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:90619 HCAPLUS

DOCUMENT NUMBER: 136:112708

TITLE: Tacrolimus formulation for the treatment of ocular diseases

INVENTOR(S): Peyman, Gholam A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 4 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2002013340 | A1 | 20020131 | US 2000-507076 | 20000218 |
| US 6489335 | B2 | 20021203 | | |
| US 2003018044 | A1 | 20030123 | US 2002-247220 | 20020919 |

PRIORITY APPLN. INFO.: US 2000-507076 A2 20000218

AB A formulation to treat ocular diseases, e.g. dry eye disease, as well as other diseases, is disclosed. Tacrolimus is administered either topically or by injection. For topical administration, an amt. of about 1 ng to 10 .mu./g may be formulated in an aq. based cream that may be applied at bedtime or throughout the day. For injection, a dose of about 20-1000 .mu.g/mL is used. Tacrolimus may also be administered in milligram quantities as a surgical implant contained in a diffusible walled reservoir sutured to the wall of the sclera, or may be contained within an inert carrier such as microspheres or liposomes to provide a slow-release drug delivery system.

IT 104987-11-3, Tacrolimus

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tacrolimus formulation for treatment of ocular disease)

L12 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:667846 HCAPLUS

DOCUMENT NUMBER: 136:339

TITLE: Treatment of ocular cicatricial pemphigoid with tacrolimus (FK 506)

AUTHOR(S): Letko, Erik; Ahmed, A. Razzaque; Foster, C. Stephen

CORPORATE SOURCE: Immunology and Uveitis Service, Boston, MA, 02116, USA
SOURCE: Graefe's Archive for Clinical and Experimental

Ophthalmology (2001), 239(6), 441-444

CODEN: GACODL; ISSN: 0721-832X

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Purpose: To evaluate the efficacy of tacrolimus (FK 506) therapy in patients with ocular cicatricial pemphigoid (OCP). Methods: In a cohort study, six patients with OCP, in whom the disease was not controlled by conventional immunosuppressive agents administered in high doses for an appropriate period of time, were treated with FK 506. The FK 506 was administered orally at the daily dose of 8 mg. Final clin. response to FK 506 was divided into three categories based on the difference between severity of conjunctival inflammation before and after FK 506 therapy. "Total control" of disease activity was defined as residual inflammatory activity of 0.5 or less in the final examn. and an inflammation decrement of at least 0.5 between initial and final examn. "Partial control" was defined as final disease activity 1.0 or 1.5 and at least 0.5 decrement of disease activity between initial and final examn. "Uncontrolled inflammation" was defined as final disease activity above 1.5 or no improvement between initial and final activity. Results: The av. age of the patients was 67.5 yr (range 50-75 yr). Male to female ratio was 1:1. The av. duration of OCP prior to beginning of FK 506 treatment was 6.25 yr (range 3-12.5 yr). The av. duration of treatment with FK 506 was 11 mo (range 5-18 mo). The av. disease activity prior to the administration of FK 506 was 2.6 (range 2.0-3.0). The av. disease activity at the time when FK 506 was stopped was 2.0 (range 1.0-2.5). In four patients (67%) FK 506 failed to control activity of OCP, and in two patients (33%) the activity was controlled partially. Conclusions: Although FK 506 was not used in a prospective randomized trial and although the authors used the drug only in patients with OCP refractory to conventional immunosuppressive agents, it is likely that FK 506 is incapable of controlling the activity of OCP and inducing a remission.

IT 104987-11-3, FK 506

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(tacrolimus is ineffective in treatment of **ocular** cicatricial pemphigoid in humans)

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2001:319758 HCAPLUS
 DOCUMENT NUMBER: 134:331600
 TITLE: Use of a CD40:CD154 binding interruptor to treat immunological complications of the eye
 INVENTOR(S): Dana, M. Reza; Vaishnav, Akshay K.; Burkly, Linda C.; Lobb, Roy; Adelman, Burt
 PATENT ASSIGNEE(S): Biogen, Inc., USA; Schepens Eye Research Institute
 SOURCE: PCT Int. Appl., 78 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|---|----------|-----------------|----------|
| WO 2001030386 | A1 | 20010503 | WO 2000-US28945 | 20001019 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, | | | |

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 EP 1223981 A1 20020724 EP 2000-973678 20001019
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL
 US 2003027744 A1 20030206 US 2002-125264 20020418
 PRIORITY APPLN. INFO.: US 1999-160909P P 19991022
 US 2000-196453P P 20000411
 US 2000-229491P P 20000831
 WO 2000-US28945 W 20001019

AB The invention relates generally to the treatment and inhibition of immunol. complications of the eye. Such complications include unwanted immune responses resulting in an ocular inflammatory disease, resulting from a corneal or retinal graft transplantation or resulting from ocular angiogenesis, particularly ocular neovascularization. The invention relates in particular to the inhibition, treatment, or reversal of immune-system driven rejection of grafted corneal or retinal tissue or cells in a recipient host and to the treatment or inhibition of ocular inflammatory disease or ocular neovascularization in a host. Compns. and methods disclosed herein capitalize on the discovery that immunol. complications of the eye can be inhibited using a CD40:CD154 binding interruptor, either alone or in combination with another immunomodulator or immunosuppressor. An exemplary CD40:CD154 binding interruptor is an anti-CD154 monoclonal antibody, such as an antibody having the antigen-specific binding characteristics of the 5c8 monoclonal antibody.

IT 104987-11-3, Tacrolimus
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (use of a CD40:CD154 binding interruptor to treat immunol. complications of the eye)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2001:319703 HCPLUS
 DOCUMENT NUMBER: 134:316155
 TITLE: Controlled-release biocompatible ocular drug delivery implant devices and methods
 INVENTOR(S): Wong, Vernon G.; Hu, Mae W. L.; Berger, Donald E., Jr.
 PATENT ASSIGNEE(S): Oculex Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 44 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| WO 2001030323 | A2 | 20010503 | WO 2000-US29004 | 20001019 |
| WO 2001030323 | A3 | 20020221 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
 CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 US 6331313 B1 20011218 US 1999-426141 19991022
 EP 1143935 A2 20011017 EP 2000-973704 20001019
 EP 1143935 A3 20020918
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, IE, SI,
 LT, LV, FI, RO
 BR 2000007454 A 20011030 BR 2000-7454 20001019
 NO 2001003094 A 20010822 NO 2001-3094 20010621
 PRIORITY APPLN. INFO.: US 1999-426141 A2 19991022
 WO 2000-US29004 W 20001019

AB Controlled-release devices are disclosed which are biocompatible and can be implanted into the eye. The devices have a core comprising a drug and a polymeric outer layer which is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the release of the drug during a delivery period, and drug release is affected through an orifice in the outer layer. These devices have an orifice area of less than 10% of the total surface area of the device and can be used to deliver a variety of drugs with varying degrees of solv. and or mol. wt. Methods are also provided for using these drug delivery devices. A teflon tube of 0.97 mm internal diam. and 1.31 mm outer diam. was used to prep. a cylindrical device with 5.7 mm long and comprising 3.3 mg of gentamicin.

IT 104987-11-3, Tacrolimus

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (controlled-release biocompatible **ocular** drug delivery
 implant devices having impermeable polymeric outer layers and drug
 core)

L12 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2000:790310 HCAPLUS
 DOCUMENT NUMBER: 133:317582
 TITLE: Use of macrolide compounds for the treatment of dry
 eye
 INVENTOR(S): Ueno, Ryuji
 PATENT ASSIGNEE(S): R-Tech Ueno, Ltd., Japan
 SOURCE: PCT Int. Appl., 22 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|------------|
| WO 2000066122 | A1 | 20001109 | WO 2000-JP2756 | 20000426 |
| W: AL, AU, BR, CA, CN, CZ, HU, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, RO, RU, SI, TR, US, ZA | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 1173177 | A1 | 20020123 | EP 2000-921047 | 20000426 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 2000011225 | A | 20020319 | BR 2000-11225 | 20000426 |
| JP 2002543132 | T2 | 20021217 | JP 2000-615007 | 20000426 |
| NO 2001005288 | A | 20011029 | NO 2001-5288 | 20011029 |
| PRIORITY APPLN. INFO.: | | | US 1999-132009P | P 19990430 |
| | | | WO 2000-JP2756 | W 20000426 |

OTHER SOURCE(S): MARPAT 133:317582

AB The present invention provides an agent for treating a dry eye, which contains a macrolide compd. such as FK506.

IT 104987-11-3, FK506

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(use of macrolide compds. such as FK506 for treatment of dry eye)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1999:451211 HCPLUS
 DOCUMENT NUMBER: 131:92517
 TITLE: Topical ophthalmic preparations containing immunosuppressive agents
 INVENTOR(S): Stuchlik, Milan; Jegorov, Alexandr; Matha, Vladimir;
 Stuchlik, Josef
 PATENT ASSIGNEE(S): Galena, A.S., Czech Rep.
 SOURCE: PCT Int. Appl., 26 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 9934830 | A1 | 19990715 | WO 1998-CZ54 | 19981217 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CZ 287497 | B6 | 20001213 | CZ 1997-4237 | 19971230 |
| CA 2317010 | AA | 19990715 | CA 1998-2317010 | 19981217 |
| AU 9914813 | A1 | 19990726 | AU 1999-14813 | 19981217 |
| EP 1058560 | A1 | 20001213 | EP 1998-958793 | 19981217 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI, RO | | | | |
| JP 2002500200 | T2 | 20020108 | JP 2000-527277 | 19981217 |
| NO 2000003344 | A | 20000627 | NO 2000-3344 | 20000627 |
| PRIORITY APPLN. INFO.: | | | CZ 1997-4237 | A 19971230 |
| | | | WO 1998-CZ54 | W 19981217 |

AB Disclosed are therapeutic prepns. for topical ophthalmic application, contg. 0.02-5.0 % of immunosuppressive agents belonging to the groups of monocyclic undecapeptides, macrolide lactones or corticosteroids, in a vehicle comprising up to 10 % of polyalkylene glycol-polyurethane copolymers. Said copolymers consist preferably of poly(oxy-1,2-ethanediyl)-.alpha.-hydro-.omega.-hydroxypolymers with 1,1'-methylene-bis-(4-isocyanatocyclohexane) having an av. mol. wt. of from 1000 to 3000 in a hydrophilic vehicle and preferably of poly[oxy(methyl-1,2-ethanediyl)].alpha.-hydro-.omega.-hydroxypolymers with 1,1'-methylene-bis-(4-isocyanatocyclohexane) having an av. mol. wt. of from 1600 to 18000 in a lipophilic vehicle. Said therapeutic agents can further contain addnl. excipients common in topical administration forms. An eye drop soln. contained ciclosporin 1, 4,4'-dicyclohexylmethane diisocyanate-polyethylene glycol copolymer 1, diglyceryl monooleate 2.5, chlorobutanol 0.5 kg, and maize oil to 100 L.

IT 104987-11-3, Tacrolimus

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(topical ophthalmic preps. contg. immunosuppressive agents)
 REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1999:432478 HCAPLUS
 DOCUMENT NUMBER: 131:110793
 TITLE: New topical treatments for ocular inflammatory
 disease. Cyclosporin, FK506 and NSAIDs
 AUTHOR(S): Hikita, Naofumi
 CORPORATE SOURCE: Sch. Med., Kurume Univ., Kurume, 830-0011, Japan
 SOURCE: Atarashii Ganka (1999), 16(6), 775-780
 CODEN: ATGAEX; ISSN: 0910-1810
 PUBLISHER: Medikaru Ai Shuppan
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review with 18 refs., on action mechanism and ophthalmic application of
 eye drops contg. immunosuppressants including cyclosporin, FK506, and
 FTY720, and eye drops contg. nonsteroidal antiinflammatory drugs.
 IT 104987-11-3, FK506
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)
 (topical treatment of **ocular** inflammatory diseases by
 cyclosporin, FK506, and NSAIDs)

L12 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1998:521822 HCAPLUS
 DOCUMENT NUMBER: 129:285735
 TITLE: Cytokine production by T cells infiltrating in the eye
 of uveitis patients
 AUTHOR(S): Sakaguchi, Mami; Sugita, Sunao; Sagawa, Kimitaka;
 Itoh, Kyogo; Mochizuki, Manabu
 CORPORATE SOURCE: Departments of Ophthalmology, Kurume University School
 of Medicine, Kurume, Japan
 SOURCE: Japanese Journal of Ophthalmology (1998), 42(4),
 262-268
 CODEN: JJOPA7; ISSN: 0021-5155
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The capacity of T cells to produce cytokines was investigated using T-cell
 clones (TCCs) established from infiltrating cells in the aq. humor (AH) or
 peripheral blood mononuclear cells (PBMC) of patients with
 Vogt-Koyanagi-Harada (VKH) disease or sarcoidosis. The cytokines produced
 and tested in the study were interleukin (IL)-1. α , IL-6, IL-8,
 interferon (IFN)- γ , tumor necrosis factor (TNF)- α , and
 granulocyte monocyte colony stimulating factor (GM-CSF). All TCCs (n = 9)
 from AH of VKH patients spontaneously produced significantly larger amts.
 of IL-6, IL-8, and IFN- γ than TCCs from healthy donor PBMC. All
 TCCs (n = 9) from AH of the sarcoidosis patient spontaneously produced
 significantly larger amts. of IL-1. α , IL-6, and IL-8 than TCCs from
 healthy donor PBMC. In addn., the effects of antiinflammatory drugs on
 the cytokine prodn. by the TCCs were investigated. Hydrocortisone
 significantly suppressed the prodn. of IL-6, IL-8, and GM-CSF by TCCs from
 AH of VKH patients. Tacrolimus also significantly suppressed the prodn.
 of IL-8 and GM-CSF by the TCCs. FTY720, an exptl. drug, suppressed only
 GM-CSF prodn. by TCCs from AH of VKH patients. Diclofenac failed to
 suppress the prodn. of any cytokines by any TCCs. All tested drugs did
 not suppress the prodn. of cytokines by TCCs from the sarcoidosis patient.
 These results thus suggest that cytokines produced by T cells infiltrating

in the eye may play an important role in the pathogenesis of uveitis.
 IT 104987-11-3, Tacrolimus
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (cytokine prodn. by T cells infiltrating in the eye of uveitis patients and effects of anti-inflammatory drugs)

L12 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1997:712082 HCAPLUS
 DOCUMENT NUMBER: 128:30156
 TITLE: Cataract development induced by repeated oral dosing with FK506 (tacrolimus) in adult rats
 AUTHOR(S): Ishida, Hisao; Mitamura, Takashi; Takahashi, Yuri; Hisatomi, Akihiko; Fukuhara, Yoshifumi; Murato, Kazuo; Ohara, Kaname
 CORPORATE SOURCE: Toxicology Research Lab., Fujisawa Pharmaceutical Co. Ltd., Osaka, 532, Japan
 SOURCE: Toxicology (1997), 123(3), 167-175
 CODEN: TXCYAC; ISSN: 0300-483X
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB FK506 (tacrolimus), a potent immunosuppressant, is used for inhibiting allograft rejection in the organ transplantation field. In a preclin. toxicity study in rats, FK506 induced various toxicities, including renal and pancreatic injuries. One of these toxic findings was cataract, and we have found that cataract appeared in rats dosed orally with FK506 for 13 wk and more. Therefore, to better elucidate the onset mechanism of FK506-induced cataract, we measured biochem. parameters, such as sorbitol, Na, K-ATPase and glutathione in the lens of rats. Rats were dosed with FK506 in oral daily doses of 0.2, 1 or 5 mg/kg for 13 wk, the lowest dose of which approximated the expected clin. dosage. Cataract developed in the 5-mg/kg/day group, with an incidence of 25%, whereas no cataract formation was obsd. in the 0.2- or 1-mg/kg/day groups. Five mg/kg/day led an increase of sorbitol and a decrease of reduced type glutathione, but did not affect Na,K-ATPase activity of the lens. FK506 is known to have diabetogenicity through pancreatic injury, which appears as vacuolation of islet cell in rats. Five mg/kg/day of FK506 induced an elevation of blood glucose assocd. with glucose intolerance, and decrease of both basal insulin level and insulin content in the pancreas, and the changes were in parallel with the cataract development in the present study. On the other hand, diabetic parameters did not change in the 0.2- or 1-mg/kg/day groups. These observations suggest that diabetes developed in the rats dosed with 5 mg/kg/day of FK506. Coadministration of a novel aldose reductase inhibitor, Zenarestat, at an oral dose of 50 mg/kg/day resulted in a redn. of incidence of the FK506-induced cataract and a decrease of sorbitol levels in the lens when compared to that in the lens of rats dosed with 5 mg/kg/day of FK506. These results suggest that FK506-induced cataract in rats is due to an accumulation of sorbitol in the lens, secondary to the diabetogenic effect of FK506. FK506 treatment at the doses of 0.2 and 1 mg/kg/day neither affected parameters indicative of diabetes nor induced cataract in rats, suggesting that the cataract would not develop with FK506 if diabetic parameters were kept under control.

IT 104987-11-3, FK506
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
 (eye sorbitol accumulation in cataract development induced by FK506)

L12 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:377098 HCAPLUS

DOCUMENT NUMBER: 125:26262
 TITLE: Eicosapentaenoic acid and/or docosahexaenoic acid for immunosuppressive therapy of autoimmune eye diseases
 INVENTOR(S): Yazawa, Kazuyoshi; Oono, Shigeaki; Ishioka, Misaki; Nakamura, Satoshi
 PATENT ASSIGNEE(S): Kanagawa Kagaku Kenkyusho Kk, Japan
 SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
 CODEN: JKXXAF
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|--|----------|-----------------|----------|
| JP 08092129 | A2 | 19960409 | JP 1993-275999 | 19931008 |
| PRIORITY APPN. INFO.: JP 1993-275999 19931008 | | | | |
| AB Eicosapentaenoic acid and/or docosahexaenoic acid are claimed for immunosuppressive therapy of autoimmune eye diseases. Thus, patients with uveitis were treated with the oral immunosuppressant FK 506 or cyclosporin A combined with fish oil contg. 6% eicosapentaenoic acid and 25% docosahexaenoic acid with satisfactory results. | | | | |
| IT 104987-11-3, FK 506 | RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (eicosapentaenoic acid and/or docosahexaenoic acid for immunosuppressive therapy of autoimmune eye diseases) | | | |

L12 ANSWER 17 OF 27 HCPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:375747 HCPLUS
 DOCUMENT NUMBER: 125:48727
 TITLE: In vitro effects of immunosuppressive agents on cytokine production by HTLV-infected T cell clones derived from the ocular fluid of patients with HTLV-1 uveitis
 AUTHOR(S): Sagawa, Kmitaka; Mochizuki, Manabu; Katagiri, Kazuko; Tsuboi, Izumi; Sugita, Sunao; Mukaida, Naofumi; Itoh, Kyogo
 CORPORATE SOURCE: Dep. Immunol. Transfusion Med. Ophthalmol., Kurume Univ. Sch. Med., Fukuoka, 830, Japan
 SOURCE: Microbiology and Immunology (1996), 40(5), 373-379
 CODEN: MIIMDV; ISSN: 0385-5600
 PUBLISHER: Center for Academic Publications Japan
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The present study was designed to investigate the in vitro effects of potential therapeutic agents on cytokine prodn. by five HTLV-I-infected T cell clones (TCC) established from the ocular fluid of patients with HTLV-I uveitis. Each of the five HTLV-I-infected TCC was cultured at 1.times.10⁶ cells/mL with or without an immunosuppressive agent (hydrocortisone, FK506, rapamycin, indomethacin, or prostaglandin E2) for 22 h in humidified 5% CO₂ in air at 37 C. The prodn. of various cytokines in the culture supernatant from each TCC was measured by ELISA. The HTLV-I-infected TCC produced high amts. of IL-1.alpha., IL-3, IL-6, IL-8, TNF-.alpha., IFN-.gamma., and GM-CSF, and low but significant levels of IL-2 and IL-10 without any stimuli. Hydrocortisone severely depressed the prodn. by these TCC of all the cytokines except for IL-2, which was slightly increased. Prostaglandin E2 depressed the prodn. of IL-1.alpha., while it up-regulated the prodn. of IL-6, TNF-.alpha., and IFN-.gamma.. Rapamycin depressed the prodn. of IL-6 and TNF-.alpha., and FK506 depressed the prodn. of TNF-.alpha.. Hydrocortisone also severely depressed the cytokine prodn. by PHA-stimulated peripheral blood

mononuclear cells obtained from healthy volunteers. Of the immunosuppressive agents tested, hydrocortisone exhibited the strongest suppression of cytokine prodn. by HTLV-I-infected TCC. This result was in agreement with the in vivo effects of hydrocortisone in patients with HTLV-I uveitis. These TCC will be useful in investigating the effects of potential therapeutic agents for HTLV-I uveitis in vitro.

IT 104987-11-3, FK506

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(In vitro effects of immunosuppressive agents on cytokine prodn. by HTLV-infected T cell clones derived from the **ocular** fluid of patients with HTLV-1 uveitis)

L12 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:315411 HCAPLUS

DOCUMENT NUMBER: 120:315411

TITLE: Immunosuppressive effect of topical FK506 on penetrating keratoplasty in rats

AUTHOR(S): Hikita, Naofumi

CORPORATE SOURCE: Sch. Med., Kurume Univ., Kurume, 830, Japan

SOURCE: Kurume Igakkai Zasshi (1994), 57(1), 176-89

CODEN: KIZAAL; ISSN: 0368-5810

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Immunosuppressive effects of topical FK506 on a corneal graft rejection model in allogeneic inbred rats were investigated. Lewis rats were used for recipients and Fisher rats for donors. All rats received i.p. of FK506 (0.3 mg/kg/day) for 7 days in order to ensure baseline parameters. Rats were then assigned randomly to the treatment group (0.3% FK506) and the control (placebo) group. The eyedrops were given every 4 h for 2 wks. Corneal grafts were evaluated with clin. observation, histol. and immunohistol. studies. All the corneal grafts in the control group were rejected by day 14 after surgery while 1/3 of corneal grafts in the treated group survived by day 30 and the difference in the survival rate between the 2 groups was statistically significant ($p < 0.009$) on day 13. The immunohistochem. observations in the FK506-treated corneal grafts were characterized by reduced no. of CD4+ cells and a redn. in the expression of MHC class I antigens and MHC class II antigens and LFA-1. These data suggest that topical FK506 treatment is effective in preventing corneal graft rejection in the Lewis corneal graft model.

IT 104987-11-3, FK 506

RL: BIOL (Biological study)

(immunosuppressive effect and metab. of, in **eye** corneal allograft)

L12 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:296631 HCAPLUS

DOCUMENT NUMBER: 120:296631

TITLE: Immunotherapy in ocular diseases

AUTHOR(S): Mochizuki, Manabu

CORPORATE SOURCE: Sch. Med., Kurume Univ., Japan

SOURCE: Nippon Ganka Gakkai Zasshi (1992), 96(12), 1608-34

CODEN: NGZAA6; ISSN: 0029-0203

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Basic and clin. studies on immunotherapy in immune-mediated ocular disorders, i.e. uveitis, allograft rejection in corneal transplantation and allergic conjunctivitis, were carried out using a variety of immunosuppressants, including immunophilin ligands (FK506 and cyclosporine). In an animal model for uveitis, exptl. autoimmune uveitis

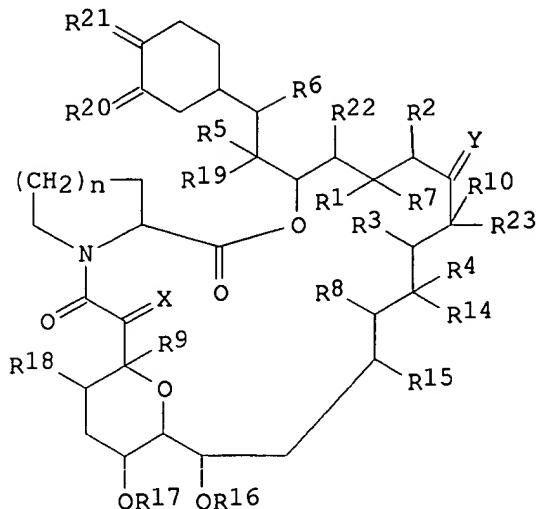
(EAU), immunophilin ligands were demonstrated in the rat and monkey to have unique immunol. activities : (1) intense and prolonged suppression of EAU development, (2) therapeutic effects by treating animals only after disease onset, (3) selective suppression on cellular immune response to S-antigen, (4) induction of immunol. tolerance and activation of antigen specific suppressor cells. Combination therapy with low doses of immunophilin ligand and other immunosuppressants was tested to achieve better effects with less side effects. A low dose of cyclosporine (2 mg/kg/day) with bucillamine (20 mg/kg/day) which suppresses antigen-presenting activity by macrophages caused much stronger suppression of EAU than the therapy with either cyclosporine or bucillamine alone. Similarly, a low dose of FK506 (0.1 mg/kg/day) with dexamethasone (0.01 mg/kg/day) caused stronger suppression of EAU. A multi-center clin. open trial of FK506 in refractory uveitis was carried out in Japan. A total of 40 cases of active uveitis in the posterior segment of the eye were treated with FK506 (0.05, 0.1 or 0.2 mg/kg/day) and the mean observation period was 26.2 wk. FK506 therapy improved uveitis in 60% of all cases including 47% of patients resistant to previous therapy with cyclosporine. FK506 significantly suppressed the no. of uveitis attacks in patients with Behcet's disease. As for the side effects, 22.5% of patients showed abnormal values of renal function on FK506. The trough level of FK506 in whole blood correlated with adverse side effects as well as with therapeutic effect on uveitis, and it should be maintained between 15 and 25 ng/mL. Studies with immunophilin ligands indicate that they are beneficial for the therapy of severe allergic conjunctivitis and for treatment of allograft rejection.

IT 104987-11-3, FK506

RL: BIOL (Biological study)
(in ocular disease and corneal allograft treatment)

L12 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:45786 HCAPLUS
DOCUMENT NUMBER: 118:45786
TITLE: Use of macrolide compounds for eye diseases,
especially allergic conjunctivitis
INVENTOR(S): Mochizuki, Manabu; Iwaki, Yoichi
PATENT ASSIGNEE(S): Kurume University, Japan
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|---------------|-----------------|----------|
| WO 9219278 | A1 | 19921112 | WO 1992-JP545 | 19920424 |
| W: CA, JP, KR, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE | | | | |
| CA 2102241 | AA | 19921027 | CA 1992-2102241 | 19920424 |
| EP 581959 | A1 | 19940209 | EP 1992-909558 | 19920424 |
| EP 581959 | B1 | 20010117 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| JP 07500570 | T2 | 19950119 | JP 1992-508698 | 19920424 |
| JP 3158437 | B2 | 20010423 | | |
| AT 198708 | E | 20010215 | AT 1992-909558 | 19920424 |
| ES 2154262 | T3 | 20010401 | ES 1992-909558 | 19920424 |
| US 5514686 | A | 19960507 | US 1994-133194 | 19940401 |
| PRIORITY APPN. INFO.: | | | | |
| | | GB 1991-9060 | A | 19910426 |
| | | GB 1991-21661 | A | 19911011 |
| | | WO 1992-JP545 | W | 19920424 |

OTHER SOURCE(S): MARPAT 118:45786
GI

AB Macrolides I [each pair of vicinal substituents (R1 and R2, R3 and R4, R6 and R21) = H pair or bond, R2 may also be alkyl; R7 = H, (protected) OH, alkoxy, or (with R1) :O; R8, R9 = H, OH; R10 = H, (hydroxy-substituted or :O-substituted) alkyl, (hydroxy-substituted) alkenyl; X = O, (H,OH), (H,H), CH2O; Y = O, (H,OH), (H,H), NNR11R12, NOR13 (R11, R12 = H, alkyl, aryl, tosyl; R13 = H, alkyl); R14-R19, R22, R23 = H, alkyl; R20, R21 = O, (R20a,H), (R21a,H) (R20a, R21a = OH, alkoxy, OCH2OCH2CH2OCH3, or R21a is protected OH, or R20a and R21a together are epoxide ring O); n = 1-3; Y, R10, R23 (with C to which they are attached) may also be 5- or 6-membered N- or S- or O-contg. (un)subst. (substituted) heterocycl], and pharmaceutically acceptable salts thereof, are disclosed for prevention or treatment of allergic conjunctivitis. Capsule and eye drop formulations of FK 506 are presented, as is the effect of FK 506 on passive anaphylaxis in rat conjunctiva..

IT 104987-11-3, FK 506

RL: BIOL (Biological study)
(eye drops and capsules of, for allergic conjunctivitis treatment)

L12 ANSWER 21 OF 27 HCPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:455982 HCPLUS

DOCUMENT NUMBER: 117:55982

TITLE: Suspensions containing tricyclic or related compounds for oral or ocular use

INVENTOR(S): Asakura, Sotoo; Koyama, Yasuto; Kiyota, Youhei; Akashi, Kiyoko; Kagayama, Akira; Murakami, Yoshio; Nakate, Toshiomi

PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan

SOURCE: Eur. Pat. Appl., 14 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.

KIND DATE

APPLICATION NO. DATE

| | | | | |
|---|----|----------|-----------------|----------|
| EP 484936 | A1 | 19920513 | EP 1991-118982 | 19911107 |
| EP 484936 | B1 | 19941005 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| CA 2054983 | AA | 19920509 | CA 1991-2054983 | 19911105 |
| RU 2079304 | C1 | 19970520 | RU 1991-5010186 | 19911106 |
| AU 9187099 | A1 | 19920514 | AU 1991-87099 | 19911107 |
| AU 653556 | B2 | 19941006 | | |
| ZA 9108846 | A | 19920826 | ZA 1991-8846 | 19911107 |
| HU 60925 | A2 | 19921130 | HU 1991-3507 | 19911107 |
| HU 210760 | B | 19950728 | | |
| ES 2061149 | T3 | 19941201 | ES 1991-118982 | 19911107 |
| CN 1061907 | A | 19920617 | CN 1991-110733 | 19911108 |
| CN 1069195 | B | 20010808 | | |
| JP 05155770 | A2 | 19930622 | JP 1991-293148 | 19911108 |
| JP 2581359 | B2 | 19970212 | | |
| IL 100011 | A1 | 19951208 | IL 1991-100011 | 19911108 |
| US 5368865 | A | 19941129 | US 1993-97617 | 19930727 |
| US 5496564 | A | 19960305 | US 1994-296403 | 19940826 |
| JP 1990-304839 A 19901108 | | | | |
| GB 1991-4834 A 19910307 | | | | |
| JP 1991-259358 A 19911007 | | | | |
| US 1991-788041 B1 19911105 | | | | |
| US 1993-97617 A1 19930727 | | | | |

PRIORITY APPLN. INFO.:

OTHER SOURCE(S): MARPAT 117:55982

AB A tricyclic compd. such as FK 506 or related compds. (Markush included) is made into suspension by addn. of a surfactant, e.g. a polyoxyethylene sorbitan fatty acid ester. The compn. can be used as an orally administrable agent or eye drops. Formulations contg. FK 506 are given, and absorption tests (for eye drop and oral compns.) are reported.

IT 104987-11-3, FK 506 104987-12-4

RL: BIOL (Biological study)
(oral or ocular pharmaceutical suspension of)

L12 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:75881 HCAPLUS

DOCUMENT NUMBER: 116:75881

TITLE: Effect of FK-506 on corneal allograft survival in the rabbit

AUTHOR(S): Kobayashi, Chihiro; Kanai, Atsushi; Nakajima, Akira

CORPORATE SOURCE: Sch. Med., Juntendo Univ., Tokyo, 113, Japan

SOURCE: Atarashii Ganka (1991), 8(11), 1771-4

CODEN: ATGAEX; ISSN: 0910-1810

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB To assess the efficacy of subconjunctivally injected FK-506 in suppressing corneal graft rejection, rabbit corneal allograft transplantation was carried out. When rekeratoplasty was performed in rabbits treated with FK-506 (0.1 mg/kg, twice a wk, for 14 wk), 8/11 were successfully transplanted and 7 of the 8 corneas kept transparency on 100th day. After exchange keratoplasties with FK-506 (0.01 mg/kg, once a wk, for 14 wk), 9/10 were successfully transplanted and all of the 9 corneas kept transparency on 200th day. When FK-506 (0.1 mg/kg) injected subconjunctivally, the concn. in anterior chamber was highest 8 h after the injection.

IT 104987-11-3, FK-506

RL: BIOL (Biological study)
(eye corneal transplant survival increase by subconjunctival)

L12 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:15272 HCAPLUS

DOCUMENT NUMBER: 116:15272
 TITLE: Cornea and aqueous humor permeability to FK-506
 eyedrops
 AUTHOR(S): Akiyama, Shuichi; Yokoyama, Toshiyuki; Kobayashi,
 Chihiro; Kanai, Atsushi; Kagayama, Akira
 CORPORATE SOURCE: Sch. Med., Juntendo Univ., Tokyo, 113, Japan
 SOURCE: Atarashii Ganka (1991), 8(9), 1445-8
 CODEN: ATGAEX; ISSN: 0910-1810
 DOCUMENT TYPE: Journal
 LANGUAGE: Japanese
 AB The soln., of FK-506, a macrolide antibiotic as an immunosuppressant
 isolated from Streptomyces, was instilled in the eyes of rabbit 10 times
 at 30 min intervals. No remarkable stimulant effect was detected by the
 Draize method. In this expt., FGK-506 was found in the cornea and iris in
 concns. of 944 and 930 ng/g, resp.
 IT 104987-11-3, FK 506
 RL: BIOL (Biological study)
 (of eye compns., after eyedrop instillation)

L12 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1991:150214 HCAPLUS
 DOCUMENT NUMBER: 114:150214
 TITLE: Aqueous liquid compositions containing
 dioxaazatricyclooctacosenetetraones
 INVENTOR(S): Honbo, Toshiyasu; Tanimoto, Sachio; Yoshida,
 Hiromitsu; Hata, Takehisa; Asakura, Sotoo; Koyama,
 Yasuto; Kiyota, Youhei
 PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
 SOURCE: Eur. Pat. Appl., 11 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 406791 | A2 | 19910109 | EP 1990-112655 | 19900703 |
| EP 406791 | A3 | 19911106 | | |
| EP 406791 | B1 | 19950201 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| AU 9058642 | A1 | 19910124 | AU 1990-58642 | 19900703 |
| AU 635286 | B2 | 19930318 | | |
| ZA 9005202 | A | 19910424 | ZA 1990-5202 | 19900703 |
| ES 2066915 | T3 | 19950316 | ES 1990-112655 | 19900703 |
| CA 2020431 | AA | 19910106 | CA 1990-2020431 | 19900704 |
| IL 94971 | A1 | 19951208 | IL 1990-94971 | 19900704 |
| CN 1048496 | A | 19910116 | CN 1990-103445 | 19900705 |
| CN 1063322 | B | 20010321 | | |
| JP 03128320 | A2 | 19910531 | JP 1990-178974 | 19900705 |
| JP 2536248 | B2 | 19960918 | | |
| US 5770607 | A | 19980623 | US 1994-276495 | 19940718 |
| JP 1989-176637 A 19890705 | | | | |
| US 1990-546883 B1 19900702 | | | | |
| US 1992-853020 B1 19920318 | | | | |

OTHER SOURCE(S): MARPAT 114:150214
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An aq. compn., such as eye drop comprises the title compds. [I; R1-R6 = H or R1R2, R3R4, and R5R6 forming bonds or R2 = alkyl; H, OH, protected OH, alkoxy or R1R7 = O; R8, R9 = OH; R10 = H, (un)substituted alkyl, etc.; X = O, CH2O, (H,OH), (H,H); Y = O, (H,OH), (H,H), NNR11R12, NOR13, etc.; R11, R12 = H, alkyl, aryl, tosyl; R13 - R19, R22, R23 = H, alkyl; R20, R21 = O, (OH, H), (alkoxy, H), etc.; n = 1-3] and a solubilizer, such as cellulose derivs. I have immunosuppressive and antimicrobial activities (no data given). An aq. eye drop contained FK 506 (II) 100, hydroxypropyl Me cellulose 350, Na2HPO4 18.4, NaH2PO4 1547, phosphate 0.32, NaCl 288, benzalkonium chloride 20 mg, and water to 100 mL.

IT 104987-11-3, FK 506

RL: BIOL (Biological study)
(eye drops contg.)

L12 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:55455 HCAPLUS
 DOCUMENT NUMBER: 114:55455
 TITLE: Effects of FK-506 and cyclosporin A on the survival of corneal grafts in rabbits
 AUTHOR(S): Kobayashi, Chihiro
 CORPORATE SOURCE: Sch. Med., Juntendo Univ., Tokyo, 113, Japan
 SOURCE: Juntendo Igaku (1990), 36(2), 189-96
 CODEN: JUIZAG; ISSN: 0022-6769

DOCUMENT TYPE: Journal
 LANGUAGE: Japanese

AB The effects on subconjunctival injection of FK-506 and cyclosporin A eyedrops after corneal allograft transplant surgery are described. In rabbits treated with FK-506, the survival rate after exchange keratoplasty (0.1 mg/kg, twice a week) was 100% on day 100 after re-keratoplasty (0.1 mg/kg, twice a week) 88% on day 100 and after exchange keratoplasty (0.01 mg/kg, once a week) 100% on day 200. In rabbits treated with cyclosporin A, the survival rate after exchange keratoplasty (0.025%, 4 times a day) was 100% on day 100 and after re-keratoplasty (0.025%, 4 times a day) 66% on day 40.

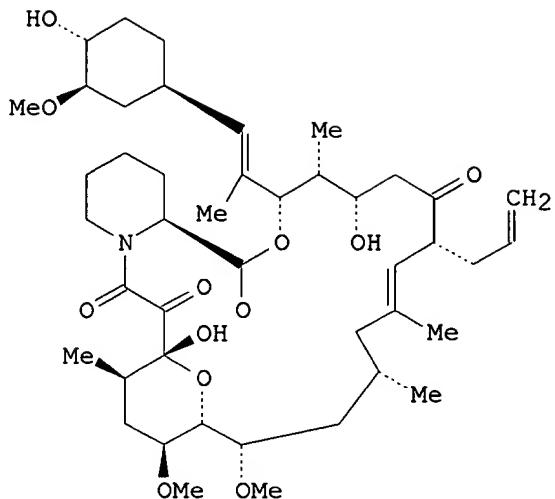
IT 104987-11-3, FK-506

RL: BIOL (Biological study)
(eye cornea transplant survival increase by)

L12 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1989:489968 HCAPLUS
 DOCUMENT NUMBER: 111:89968
 TITLE: Suppression of corneal graft rejection in rabbits by a new immunosuppressive agent, FK-506
 AUTHOR(S): Kobayashi, C.; Kanai, A.; Nakajima, A.; Okumura, K.
 CORPORATE SOURCE: Dep. Ophthalmol., Juntendo Univ., Tokyo, 113, Japan
 SOURCE: Transplantation Proceedings (1989), 21(1, Book 3), 3156-8
 CODEN: TRPPA8; ISSN: 0041-1345

DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB In rabbits with corneal grafts, topical administration of FK-506 (I) by subconjunctival injection inhibited the allograft rejection. In addn., I showed no ocular toxicity.

IT 104987-11-3, FK-506

RL: BIOL (Biological study)
(eye cornea graft rejection inhibition by)

L12 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1988:431719 HCAPLUS

DOCUMENT NUMBER: 109:31719

TITLE: Effect of FK-506 on the survival of corneal grafts in rabbits

AUTHOR(S): Kobayashi, Chihiro; Kanai, Atsushi; Shu, Shityu; Nakajima, Akira; Okumura, Ko; Iwasaki, Kazuhide

CORPORATE SOURCE: Sch. Med., Juntendo Univ., Tokyo, 113, Japan

SOURCE: Atarashii Ganka (1988), 5(2), 277-80

CODEN: ATGAEX; ISSN: 0910-1810

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB The survival rates of grafts in the treated and control groups 100 days after surgery were 100% and 25%, resp. No toxicity attributable to the drug was obsd.

IT 104987-11-3, FK 506

RL: BIOL (Biological study)
(eye cornea transplant survival response to)

=>

=> select hit rn 112 1-27

E1 THROUGH E12 ASSIGNED

=> fil reg

FILE 'REGISTRY' ENTERED AT 12:03:47 ON 26 FEB 2003

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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STRUCTURE FILE UPDATES: 25 FEB 2003 HIGHEST RN 494824-56-5
 DICTIONARY FILE UPDATES: 25 FEB 2003 HIGHEST RN 494824-56-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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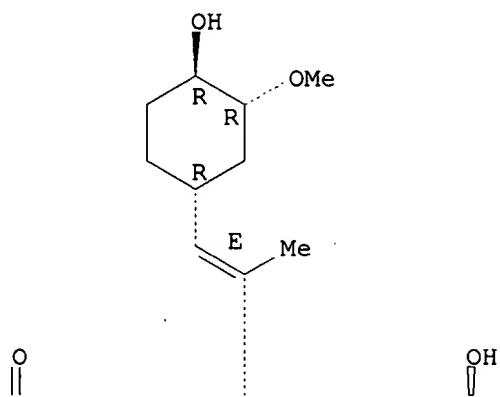
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  5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
  methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-
  propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]-
  , 2-(2-pyridinylidithio)ethyl ester (9CI)  (CA INDEX NAME)
FS STEREOSEARCH
MF C52 H78 N4 O13 S2
SR CA
LC STN Files: CAPLUS

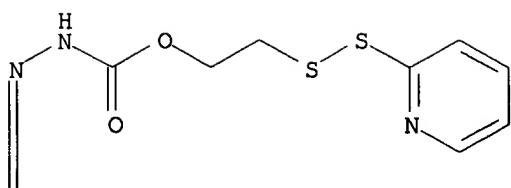
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Absolute stereochemistry.
Double bond geometry as described by E or Z.

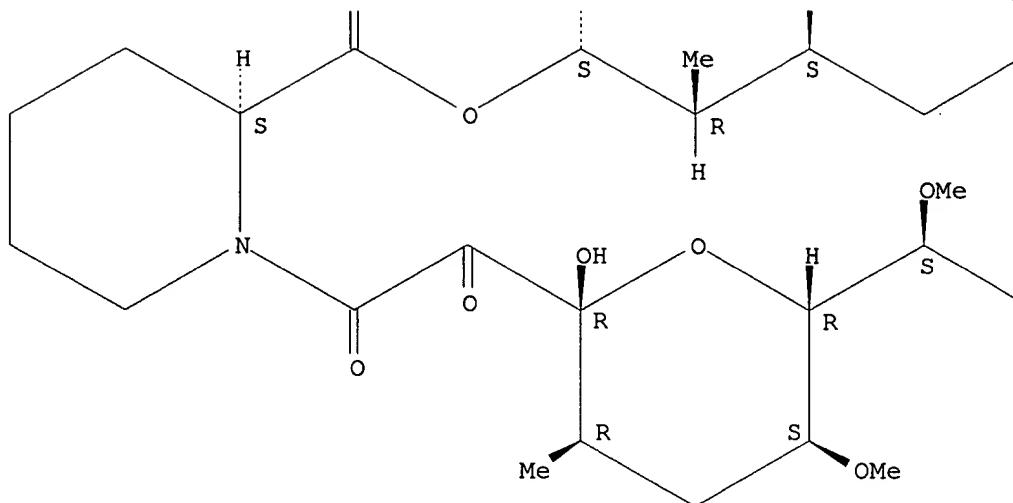
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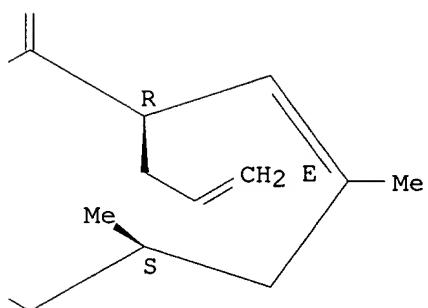
PAGE 1-B



PAGE 2-A



PAGE 2-B



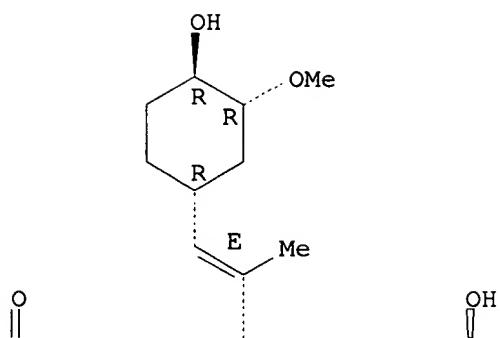
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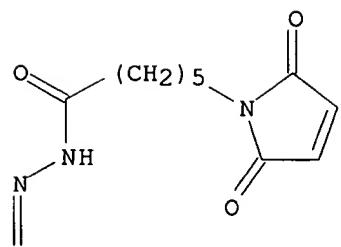
L13 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2003 ACS
 RN 491875-85-5 REGISTRY
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 SR CA
 LC STN Files: CAPLUS

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

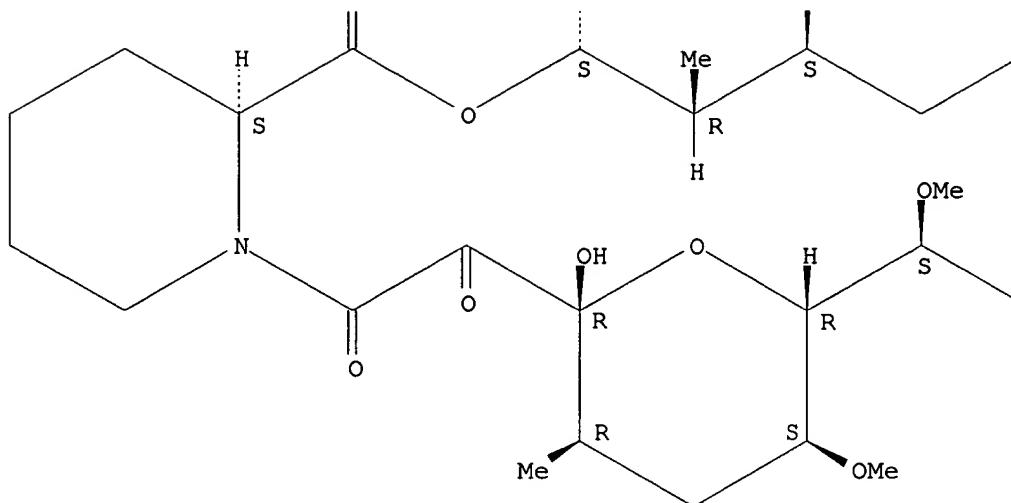
PAGE 1-A



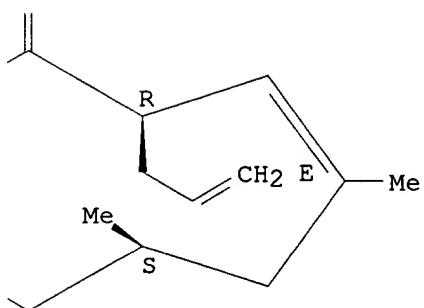
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PAGE 2-A



PAGE 2-B



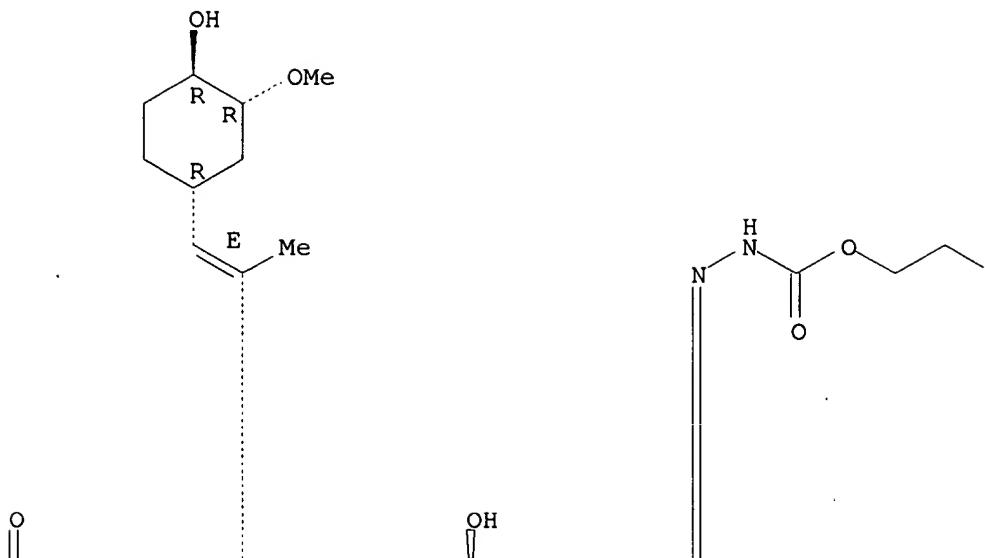
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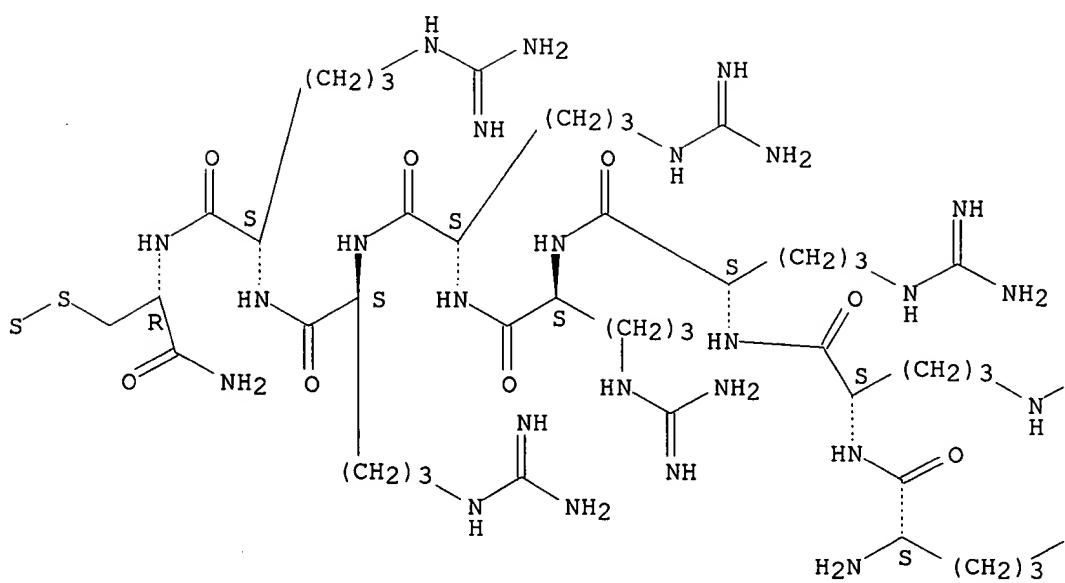
L13 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2003 ACS
 RN 491875-84-4 REGISTRY
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 FS STEREOSEARCH
 MF C92 H165 N33 O21 S2
 SR CA
 LC STN Files: CAPLUS

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

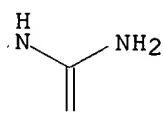
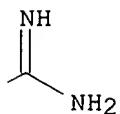
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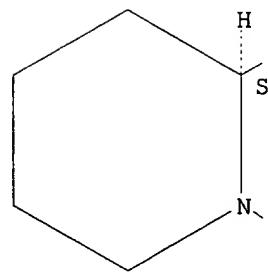
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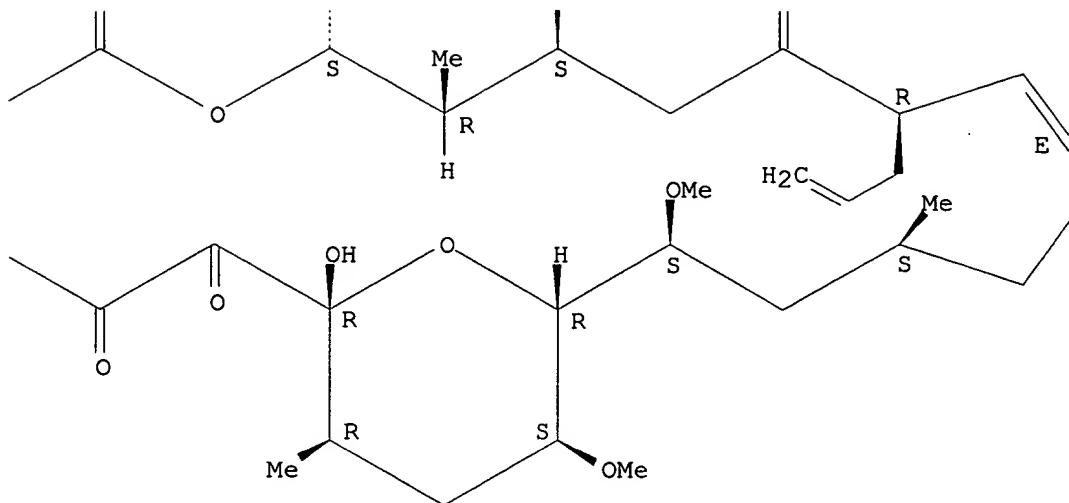
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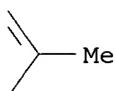
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PAGE 2-D

NH

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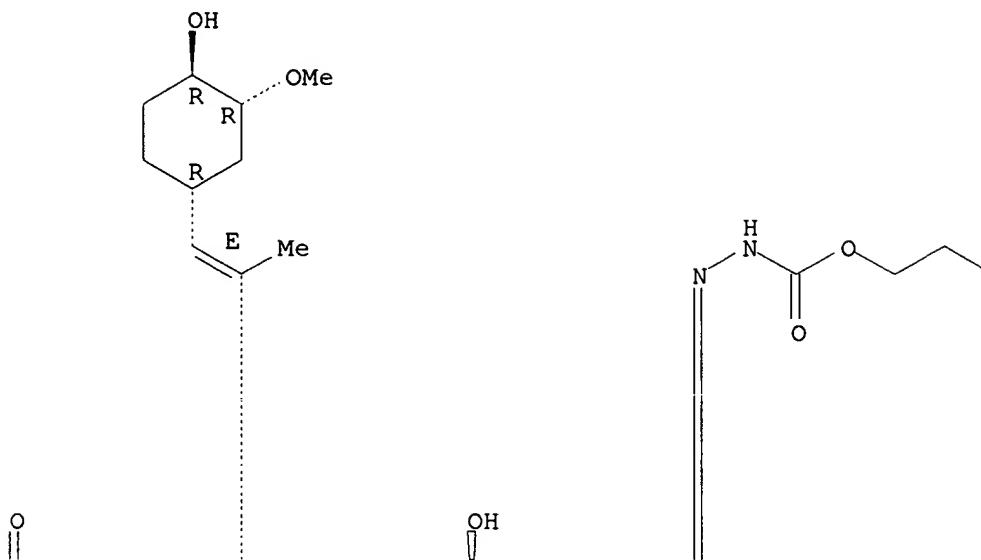
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 FS STEREOSEARCH
 MF C92 H165 N33 O21 S2
 SR CA
 LC STN Files: CAPLUS

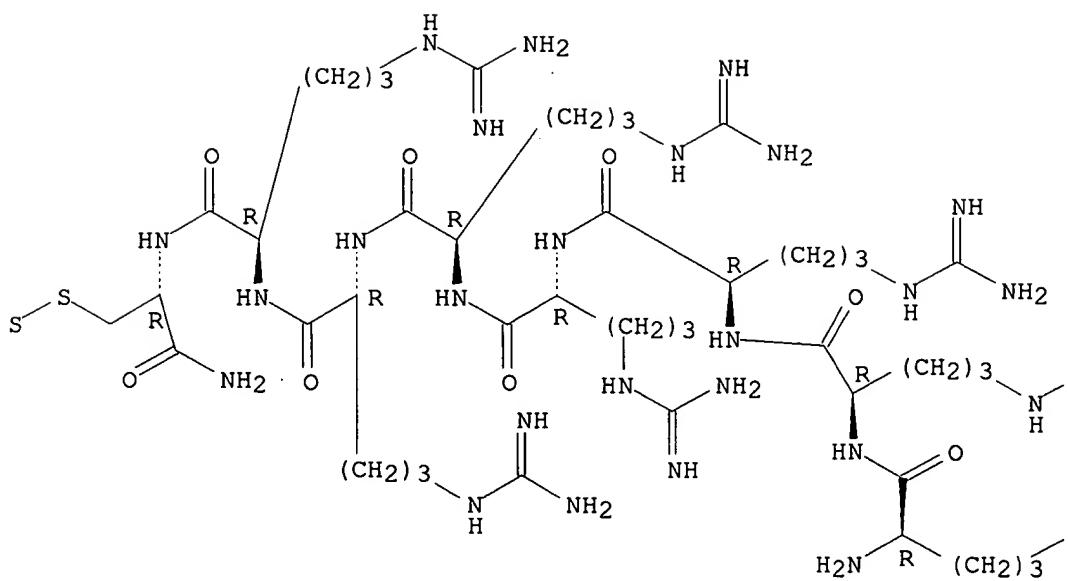
Absolute stereochemistry.

Double bond geometry as described by E or Z.

PAGE 1-B

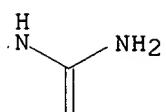
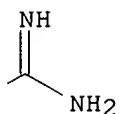


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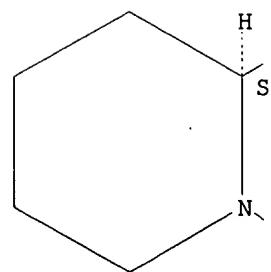


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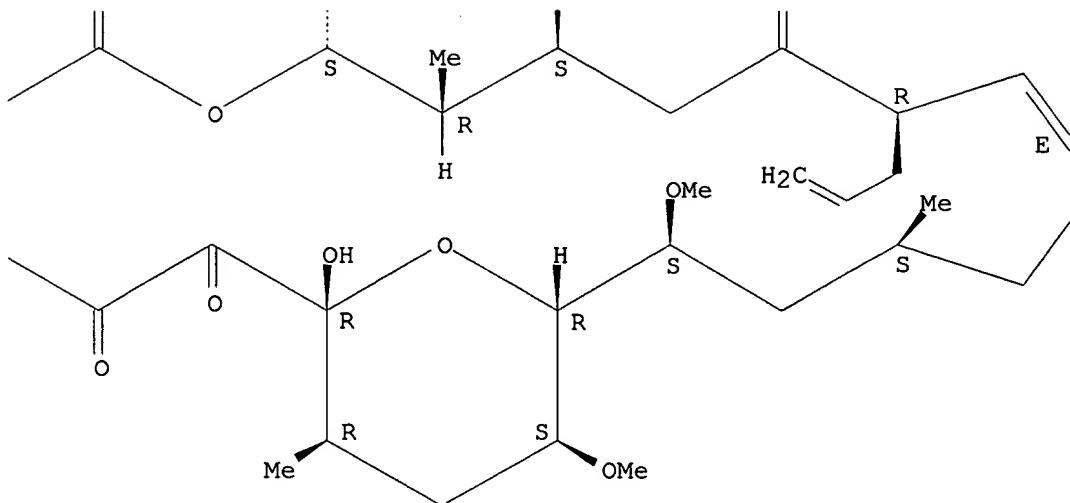
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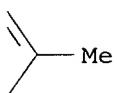
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PAGE 2-C



PAGE 2-D

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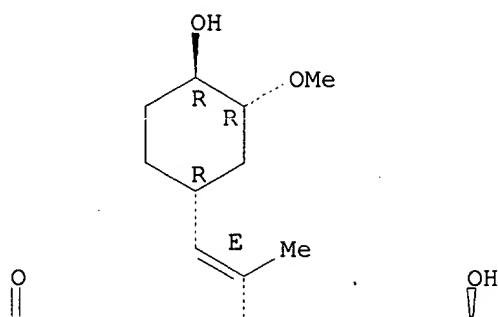
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 5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
 methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-
 propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-
 ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX
 NAME)
 FS STEREOSEARCH
 MF C99 H174 N34 O22 S
 SR CA
 LC STN Files: CAPLUS

Absolute stereochemistry.
Double bond geometry as described by E or Z.

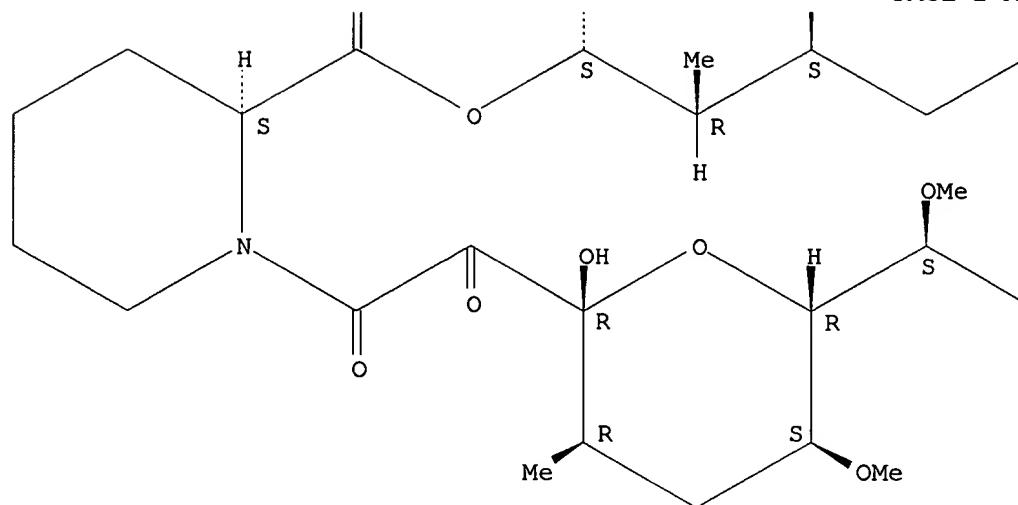
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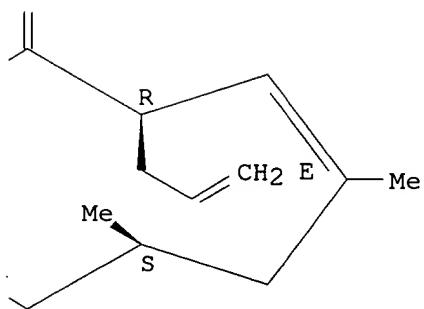
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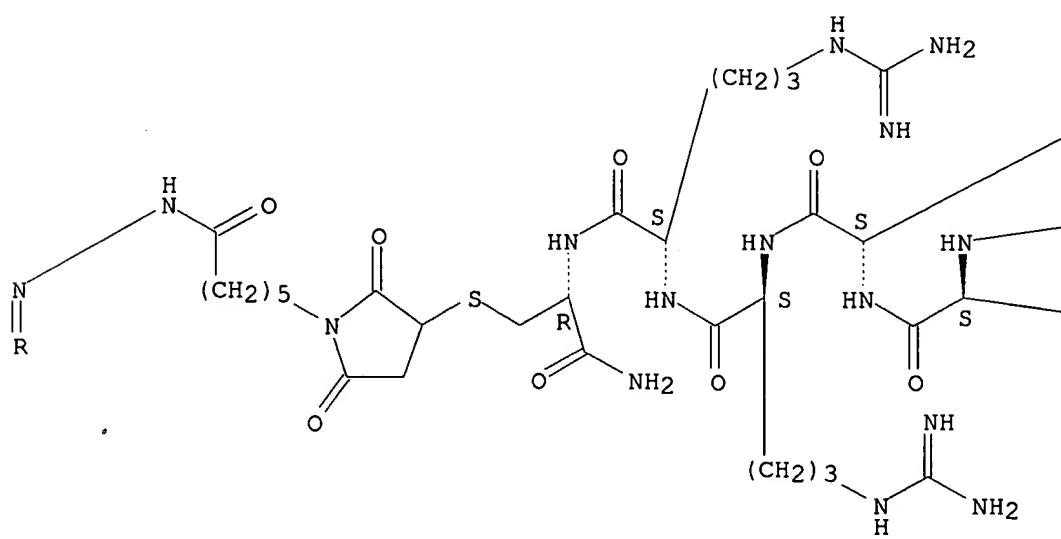
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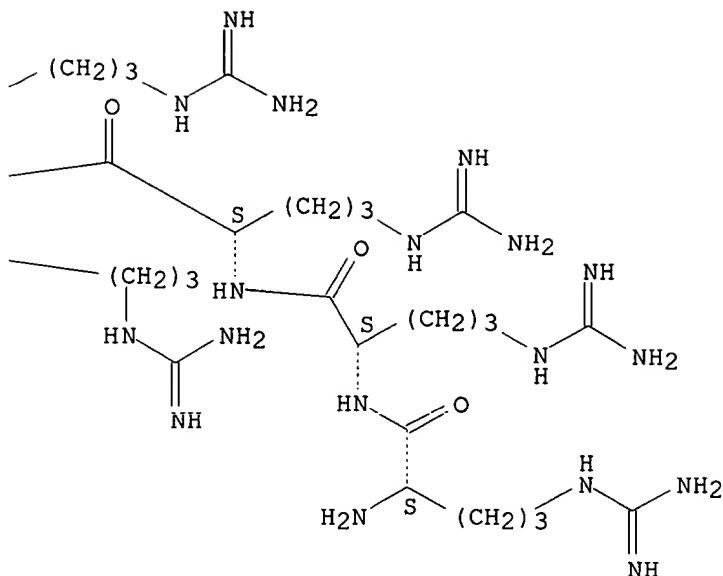


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PAGE 3-A





PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L13 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2003 ACS

RN 491875-81-1 REGISTRY

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FS STEREOSEARCH

MF C99 H174 N34 O22 S

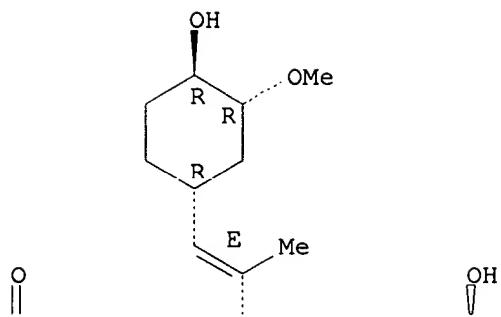
SR CA

LC STN Files: CAPLUS

Absolute stereochemistry.

Double bond geometry as described by E or Z.

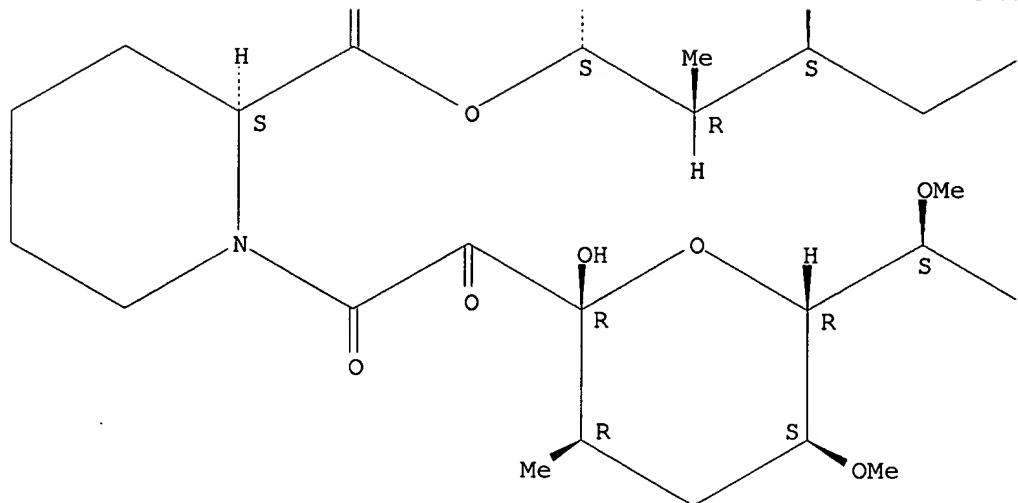
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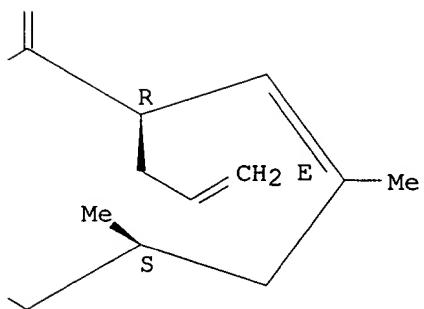
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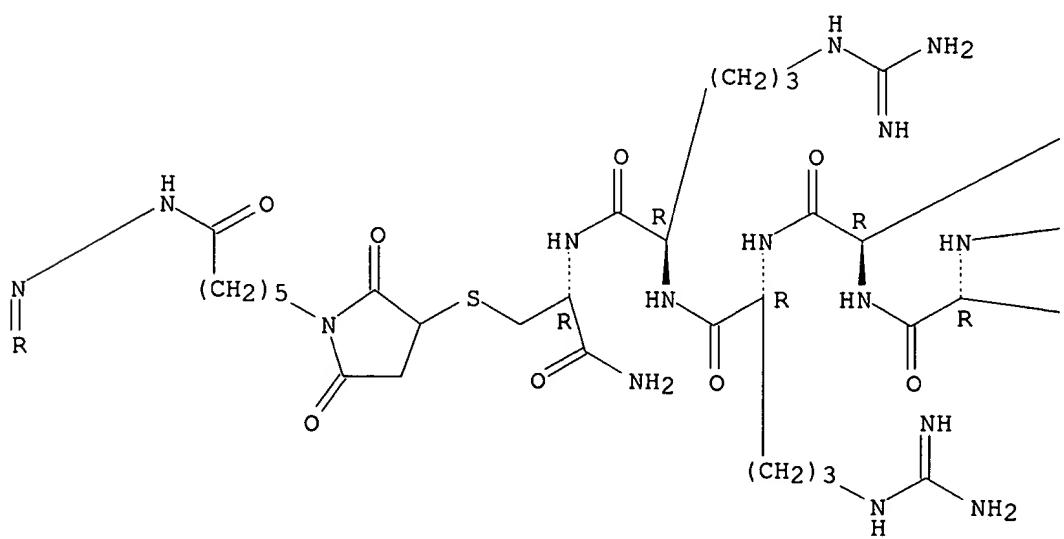
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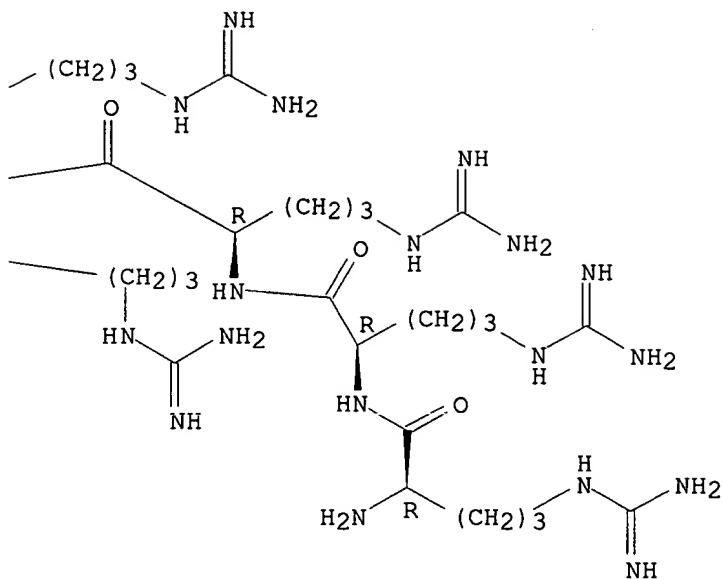


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PAGE 3-A





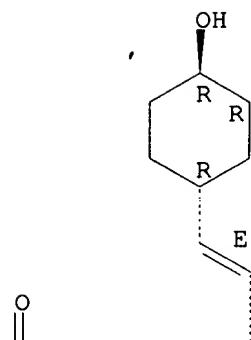
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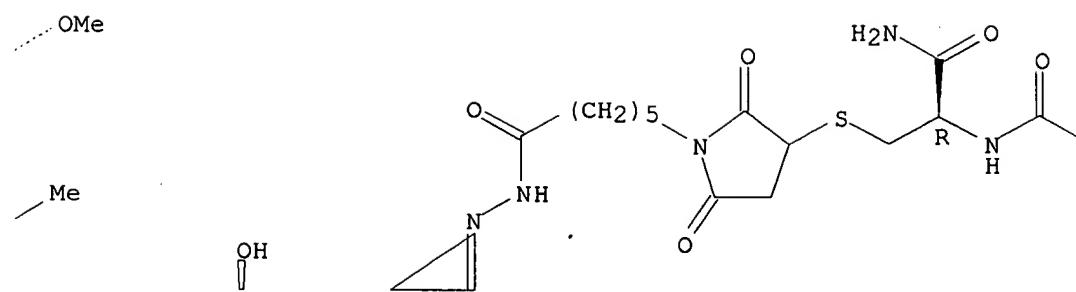
L13 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2003 ACS
 RN 491875-80-0 REGISTRY
 CN INDEX NAME NOT YET ASSIGNED
 FS STEREOSEARCH
 MF C73 H115 N9 O18 S2
 SR CA
 LC STN Files: CAPLUS

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

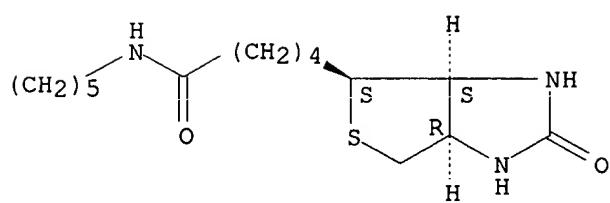
PAGE 1-A



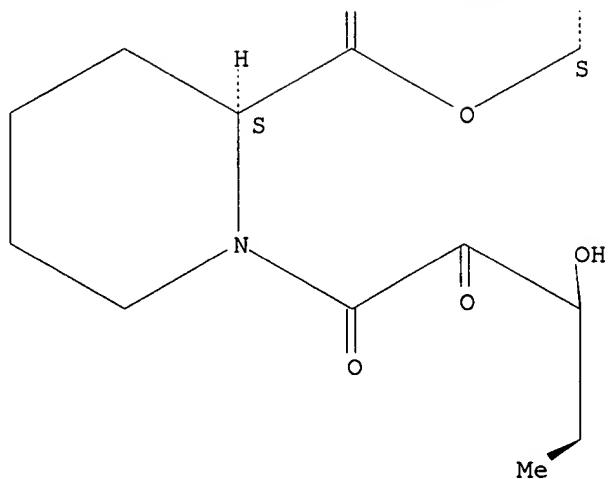
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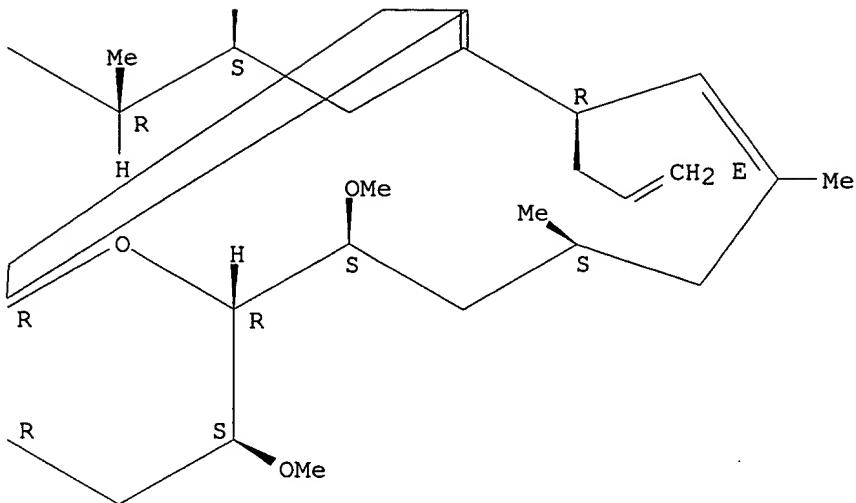
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PAGE 2-A



PAGE 2-B

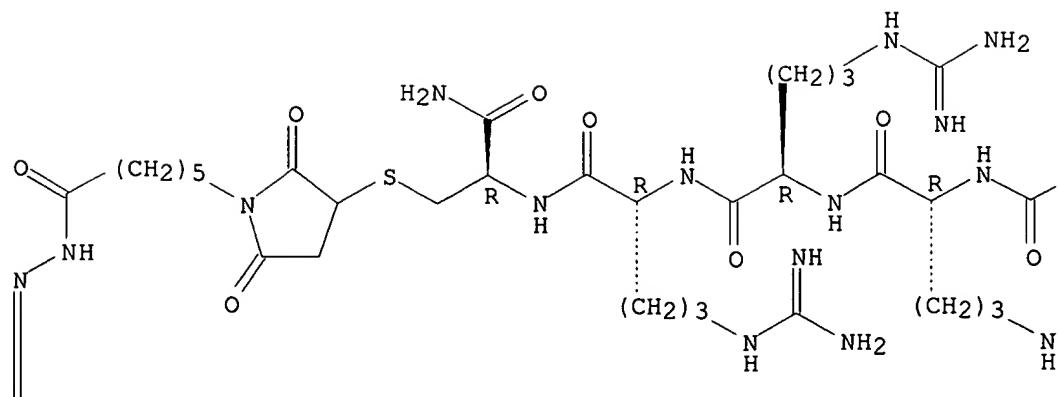
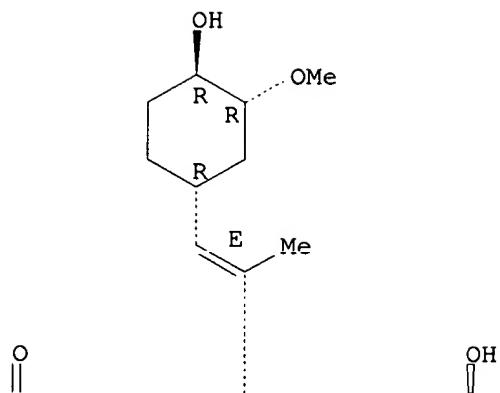


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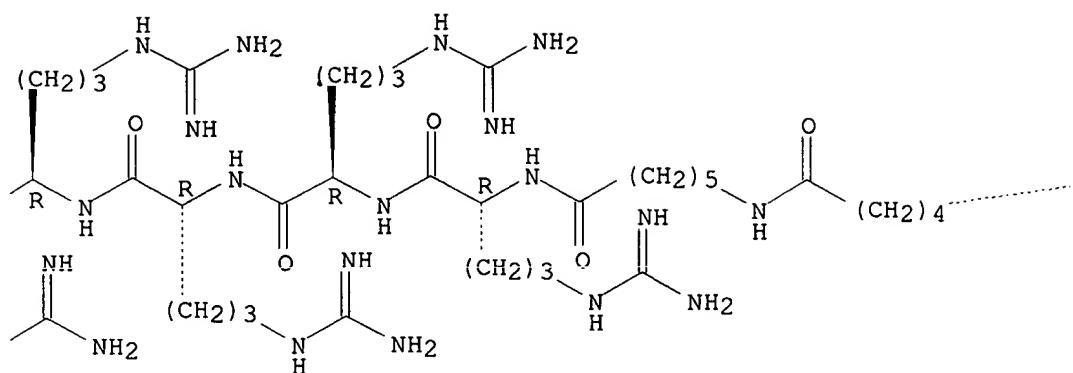
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L13 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2003 ACS
 RN 491875-79-7 REGISTRY
 CN L-Cysteinamide, N2-[6-[(5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxohexyl]-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-S-[1-[6-[(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)
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 MF C115 H199 N37 O25 S2
 SR CA
 LC STN Files: CAPLUS

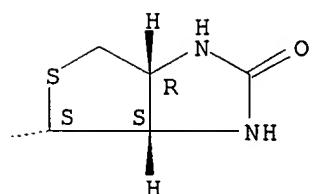
Absolute stereochemistry.
 Double bond geometry as described by E or Z.



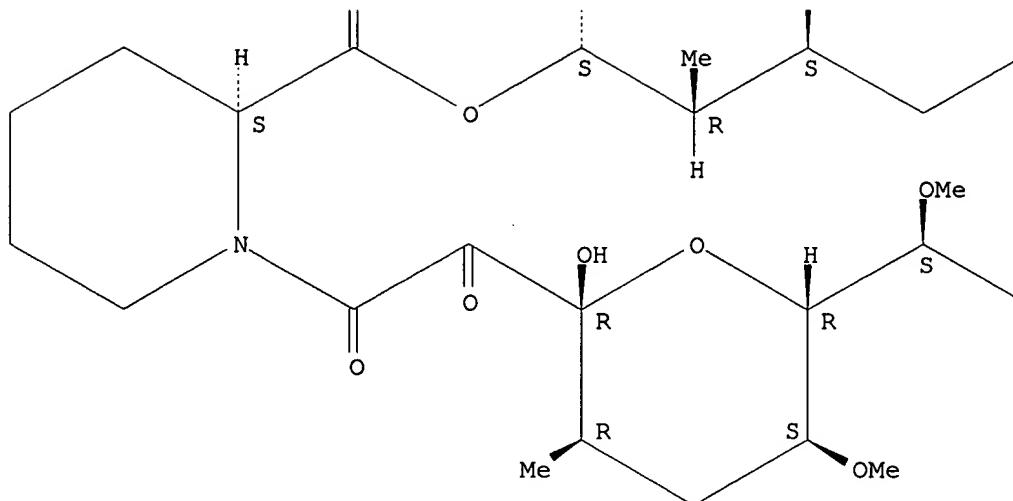
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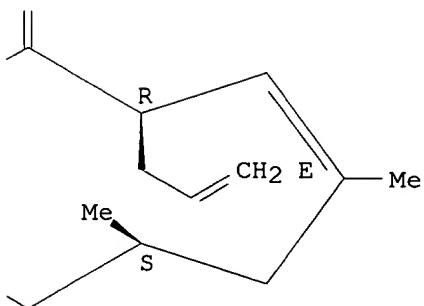
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PAGE 2-A



PAGE 2-B



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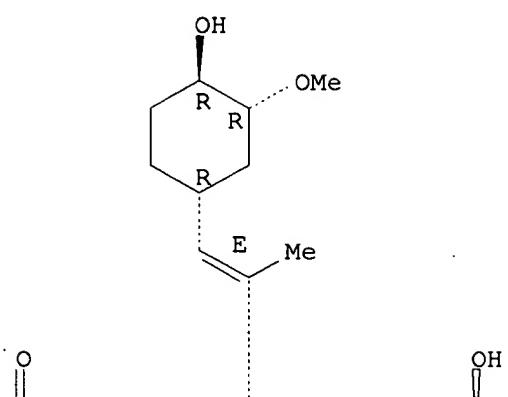
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L13 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2003 ACS
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 LC STN Files: CAPLUS

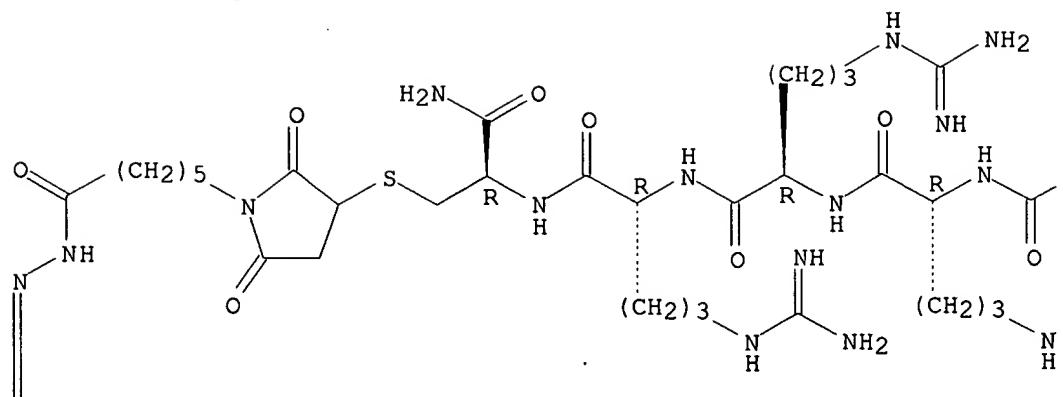
Absolute stereochemistry.

Double bond geometry as described by E or Z.

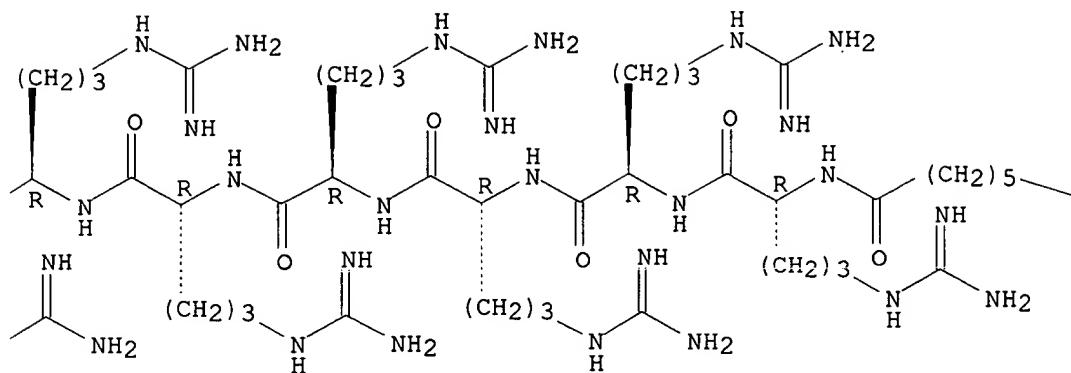
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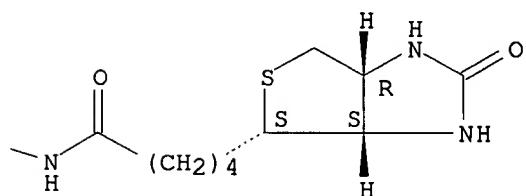
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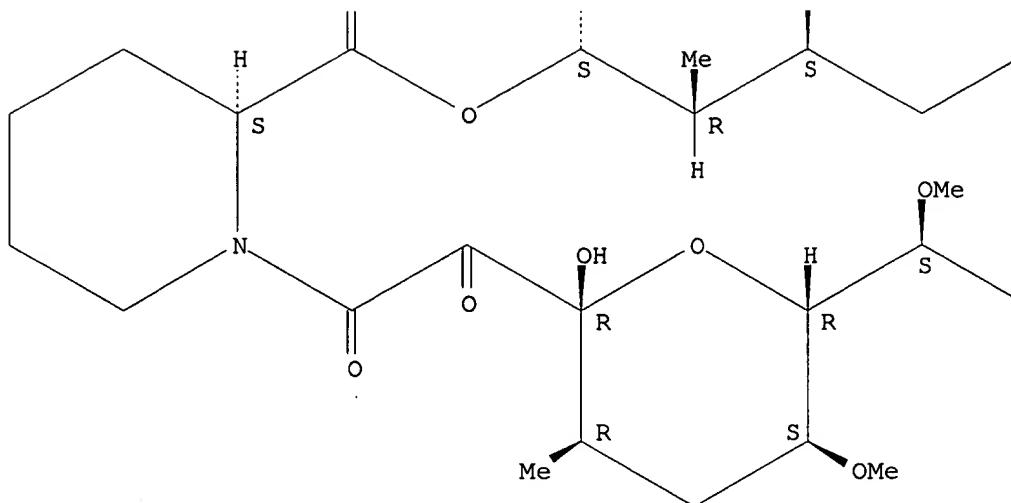
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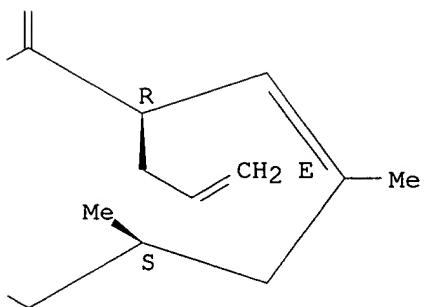
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PAGE 2-A



PAGE 2-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L13 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2003 ACS

RN 109581-93-3 REGISTRY

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OTHER CA INDEX NAMES:

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethethyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, monohydrate, [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

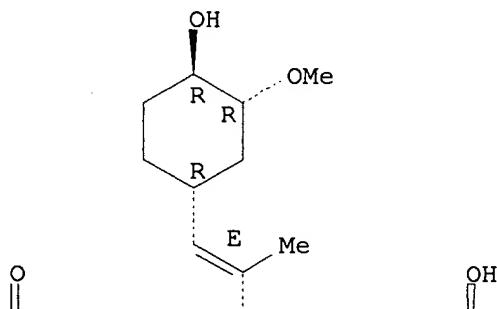
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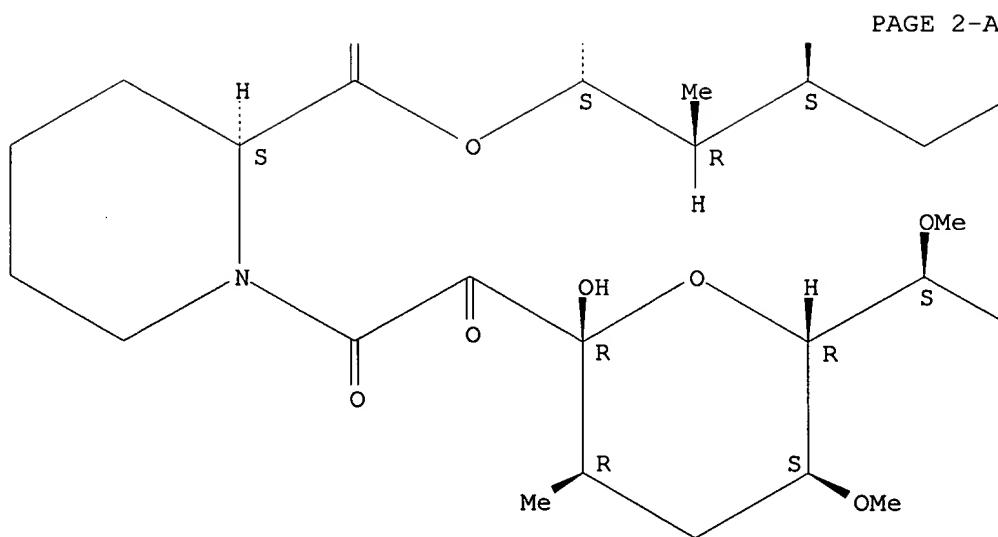
CN Tacrolimus hydrate
 CN Tsukubaenolide hydrate

FS STEREOSEARCH
MF C44 H69 N 012 . H2 O
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, CHEMCATS, CIN,
CSCHEM, DRUGPAT, DRUGUPDATES, IPA, MEDLINE, PROMT, RTECS*, SYNTHLINE,
TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
CRN (104987-11-3)

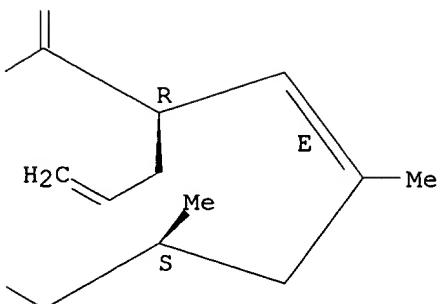
Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A





● H₂O



9 REFERENCES IN FILE CA (1962 TO DATE)
9 REFERENCES IN FILE CAPIUS (1962 TO DATE)

| | | |
|-----------|----|------------|
| REFERENCE | 1: | 138:8348 |
| REFERENCE | 2: | 136:156478 |
| REFERENCE | 3: | 134:46789 |
| REFERENCE | 4: | 133:217476 |
| REFERENCE | 5: | 131:262649 |
| REFERENCE | 6: | 130:332620 |
| REFERENCE | 7: | 127:185226 |
| REFERENCE | 8: | 126:181043 |
| REFERENCE | 9: | 107:175741 |

L13 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2003 ACS

RN 104987-12-4 REGISTRY

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

OTHER NAMES:

CN Ascomycin

CN 15000y
CN FK 520

CN FR 520

CN FR 900520

CN Immunology

SH E 33333
FS STEREOSEAR

TS STEREOGRAPH
DB 11011-38-4

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SR CA

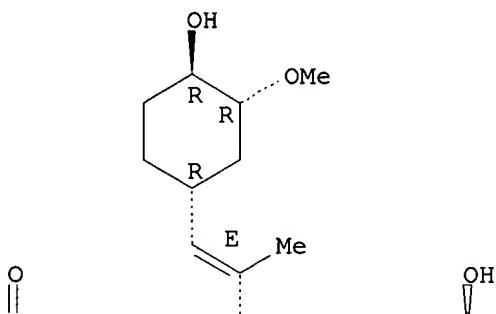
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(*File contains numerically searchable property data)

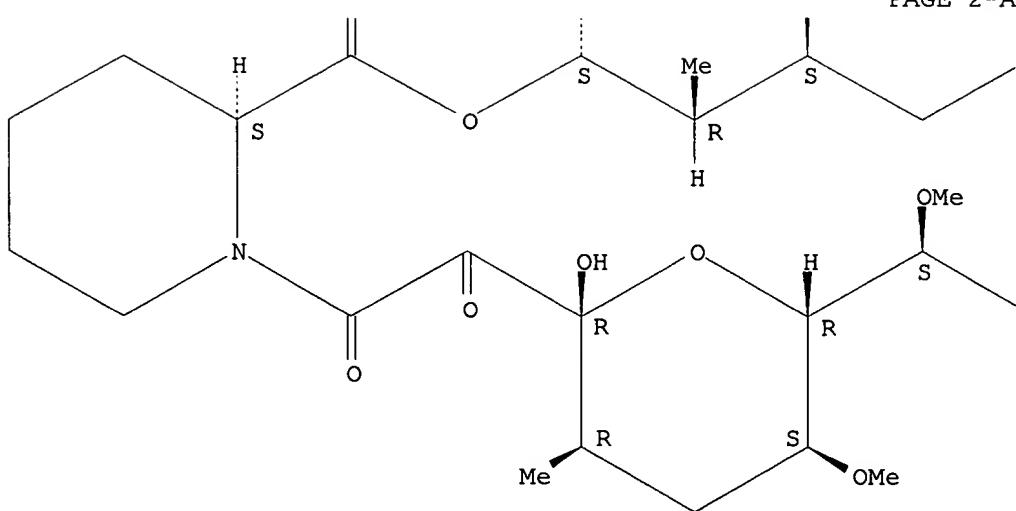
Absolute stereochemistry.

Double bond geometry as described by E or Z.

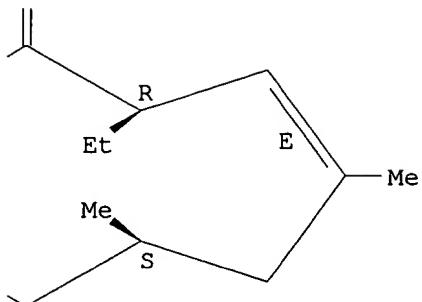
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PAGE 2-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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 38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 241 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:66697

REFERENCE 2: 138:23766

REFERENCE 3: 138:8377

REFERENCE 4: 138:8348

REFERENCE 5: 137:299948

REFERENCE 6: 137:237728

REFERENCE 7: 137:218731

REFERENCE 8: 137:215879

REFERENCE 9: 137:210973

REFERENCE 10: 137:185341

L13 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2003 ACS

RN 104987-11-3 REGISTRY

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[1(E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

OTHER NAMES:

CN (-)-FK 506

CN FK 506

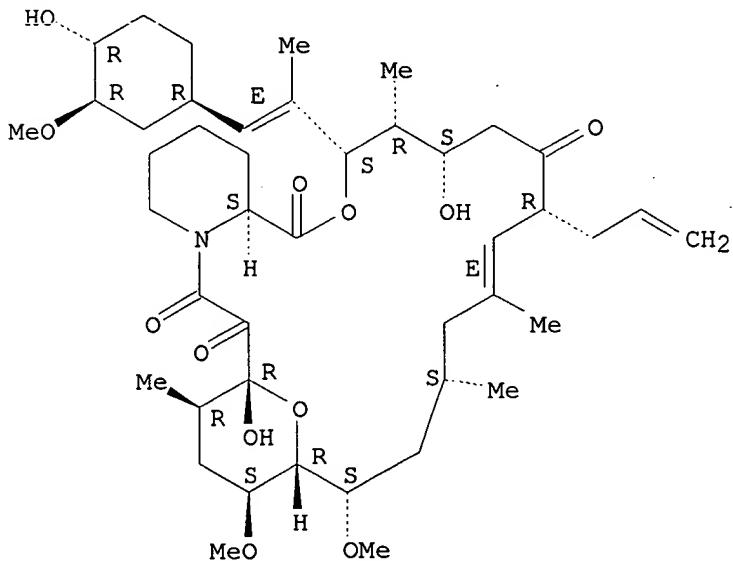
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CN Fujimycin

CN L 679934

CN Prograf
 CN Protopic
 CN Tacrolimus
 CN Tsukubaenolide
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 CI COM
 SR CA
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 BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPIUS, CASREACT, CBNB, CEN,
 CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU,
 DRUGUPDATES, EMBASE, IFICDB, IFIUDB, MEDLINE, MRCK*, PHAR, PHARMASEARCH,
 PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
 (*File contains numerically searchable property data)
 Other Sources: WHO

Absolute stereochemistry.
 Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3730 REFERENCES IN FILE CA (1962 TO DATE)
 125 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 3747 REFERENCES IN FILE CAPIUS (1962 TO DATE)

REFERENCE 1: 138:126929
 REFERENCE 2: 138:117567
 REFERENCE 3: 138:117411
 REFERENCE 4: 138:117409
 REFERENCE 5: 138:117405
 REFERENCE 6: 138:112119
 REFERENCE 7: 138:100720

REFERENCE 8: 138:100501

REFERENCE 9: 138:95621

REFERENCE 10: 138:95376

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d stat que nos

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L7          STR
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L11         101 SEA FILE=HCAPLUS L10 AND (EYE? OR OPHTHAL? OR OCUL?)
L12         27 SEA FILE=HCAPLUS L10 (L) (EYE? OR OPHTHAL? OR OCUL?)
L14         7 SEA FILE=HCAPLUS L11 AND DRY
L15         3 SEA FILE=HCAPLUS L14 NOT L12

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L15 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:696457 HCAPLUS
DOCUMENT NUMBER: 137:237728
TITLE: Peptide conjugates for enhancing drug delivery across
       and into epithelial tissues
INVENTOR(S): Rothbard, Jonathan B.; Wender, Paul A.; McGrane, P.
              Leo; Sista, Lalitha V. S.; Kirschberg, Thorsten A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 80 pp., Cont.-in-part of U.S.
         Ser. No. 648,400.
         CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

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| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| US 2002127198 | A1 | 20020912 | US 2001-792480 | 20010223 |
| WO 2002067917 | A1 | 20020906 | WO 2002-US5804 | 20020225 |
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| WO 2002069930 | A1 | 20020912 | WO 2002-US5829 | 20020225 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

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|------------------------|----|----------|-----------------|-------------|
| US 2003022831 | A1 | 20030130 | US 2002-83960 | 20020225 |
| PRIORITY APPLN. INFO.: | | | US 1999-150510P | P 19990824 |
| | | | US 2000-648400 | A2 20000824 |
| | | | US 2001-792480 | A 20010223 |

OTHER SOURCE(S): MARPAT 137:237728

AB This invention provides compns. and methods for enhancing delivery of drugs and other agents across epithelial tissues, including the skin, gastrointestinal tract, pulmonary epithelium, **ocular** tissues and the like. The compns. and methods are also useful for delivery across endothelial tissues, including the blood brain barrier. The compns. and methods employ a delivery enhancing transporter that has sufficient guanidino or amidino side-chain moieties to enhance delivery of a compd. conjugated to the reagent across one or more layers of the tissue, compared to the non-conjugated compd. The delivery-enhancing polymers include, for example, poly-arginine mols. that are preferably between about 6 and 25 residues in length. E.g., biotinylated polymers of D-arginine were prepd. and their penetration into the skin of nude mice studied.

IT 104987-11-3, FK 506

RL: RCT (Reactant); RACT (Reactant or reagent)
(peptide conjugates for enhancing drug delivery across and into epithelial tissues)

IT 455282-21-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(peptide conjugates for enhancing drug delivery across and into epithelial tissues)

IT 455282-16-3P 455282-17-4P 455282-18-5P

455282-19-6P 455282-20-9P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(peptide conjugates for enhancing drug delivery across and into epithelial tissues)

IT 104987-12-4, Ascomycin

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide conjugates for enhancing drug delivery across and into epithelial tissues)

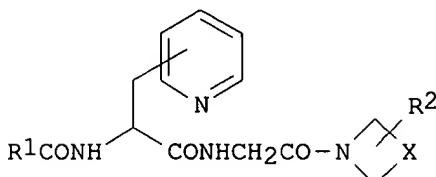
L15 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:539697 HCAPLUS
DOCUMENT NUMBER: 137:94011
TITLE: Preparation of peptide compounds having NOS inhibiting activity
INVENTOR(S): Shima, Ichiro; Ohkawa, Takehiko; Sato, Kentaro;
Ishibashi, Naoki; Imamura, Kenichiro
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2002055541 | A2 | 20020718 | WO 2001-JP11067 | 20011218 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, | | | | |

UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 PRIORITY APPLN. INFO.: AU 2001-2371 A 20010102
 AU 2001-7506 A 20010905

OTHER SOURCE(S): MARPAT 137:94011
 GI



I

AB Peptides I (R1 = halobenzofuranyl or halostyryl; R2 = substituted hydroxy, mercapto, or sulfonyl; X = CH₂, CH₂CH₂, CH₂CH₂CH₂) or their pharmaceutically acceptable salts were prepd. for the prevention and/or treatment of nitric oxide-mediated diseases. Thus, 5-chloro-N-[(1S)-2-oxo-2-[(2-oxo-2-[(1,3-thiazol-2-yloxy)-1-piperidinyl]ethyl]amino]-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide (II) was prepd. via amidation reaction and showed 100% inhibition of nitric acid. The combination of compds. I and FK507 dramatically prolonged graft survival in rat cardiac allograft.

IT 104987-11-3, Fk506

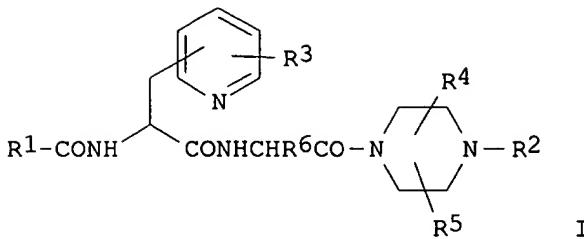
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (prepn. of peptide compds. having NOS inhibiting activity)

L15 ANSWER 3 OF 3 HCPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:338558 HCPLUS
 DOCUMENT NUMBER: 134:340709
 TITLE: Preparation of substituted dipeptides having NOS inhibiting activity
 INVENTOR(S): Shima, Ichiro; Ohkawa, Takehiko; Ohne, Kazuhiko; Sato, Kentaro; Ishibashi, Naoki; Imamura, Kenichiro
 PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
 SOURCE: PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|-------------------|----------|-----------------|------------|
| WO 2001032690 | A1 | 20010510 | WO 2000-JP7579 | 20001027 |
| W: BR, CA, CN, JP, KR, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 1226159 | A1 | 20020731 | EP 2000-970164 | 20001027 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY | | | | |
| PRIORITY APPLN. INFO.: | | | AU 1999-3868 | A 19991104 |
| | | | WO 2000-JP7579 | W 20001027 |
| OTHER SOURCE(S): | MARPAT 134:340709 | | | |

GI



AB Dipeptides I [R1 is benzofuranyl or styryl substituted by halogen; R2 is (un)substituted Ph, pyridyl, thienyl, or thiazolyl; R3, R6 = H or lower alkoxy; R4, R5 = H, lower alkyl or optionally protected hydroxy(lower)alkyl] or their pharmaceutically acceptable salts were prep'd. for use in the prevention and/or treatment of nitric oxide-mediated diseases. Thus, 5-chloro-N-[(1S)-2-[[2-[4-(4-chlorophenyl)-1-piperazinyl]-2-oxoethyl]amino]-2-oxo-1-(2-pyridylmethyl)ethyl]-1-benzofuran-2-carboxamide (II) was prep'd. via amidation reaction and showed 100% inhibition of nitric acid. The combination of compd. II and FK507 dramatically prolonged graft survival in rat cardiac allograft.

IT 104987-11-3, Fk506

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of substituted dipeptides having NOS inhibiting activity)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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E13 THROUGH E20 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 12:08:15 ON 26 FEB 2003
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STRUCTURE FILE UPDATES: 25 FEB 2003 HIGHEST RN 494824-56-5
DICTIONARY FILE UPDATES: 25 FEB 2003 HIGHEST RN 494824-56-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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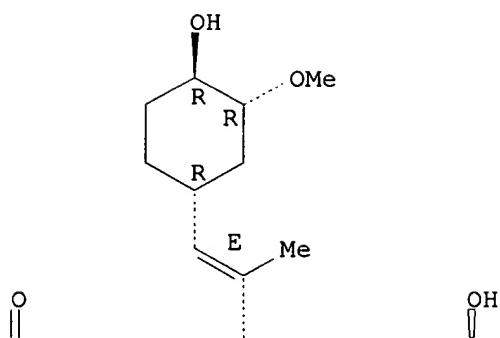
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1 455282-19-6/BI
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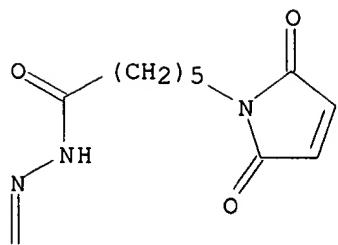
L16 ANSWER 1 OF 8 REGISTRY COPYRIGHT 2003 ACS
RN 455282-21-0 REGISTRY
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1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-
5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-
propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-
ylidene]hydrazide (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C54 H82 N4 O14
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as described by E or Z.

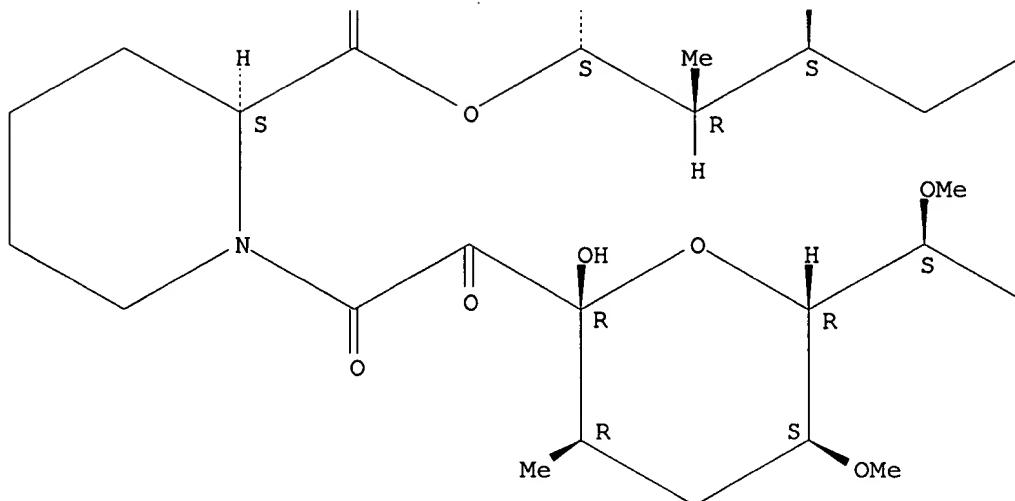
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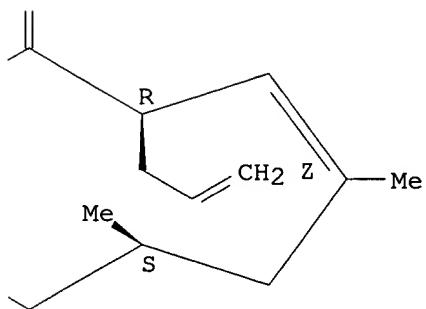
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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:237728

REFERENCE 2: 137:222033

L16 ANSWER 2 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 455282-20-9 REGISTRY

CN L-Cysteinamide, L-arginyl-L-arginyl-L-arginyl-L-arginyl-L-arginyl-L-arginyl-L-arginyl-S-[1-[6-[(3S,4R,5S,8R,9Z,12S,14S,15R,16S,18R,19R,26aS)-1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethethyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C99 H174 N34 O22 S

SR CA

Azpuru 090/926, 411

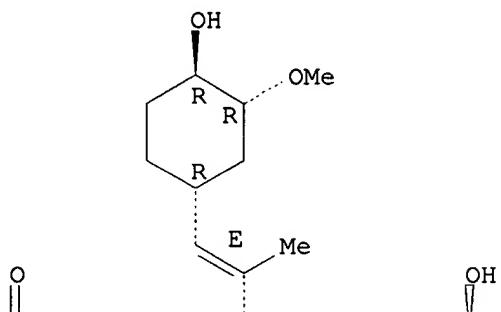
LC STN Files: CA, CAPLUS, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

Double bond geometry as described by E or Z.

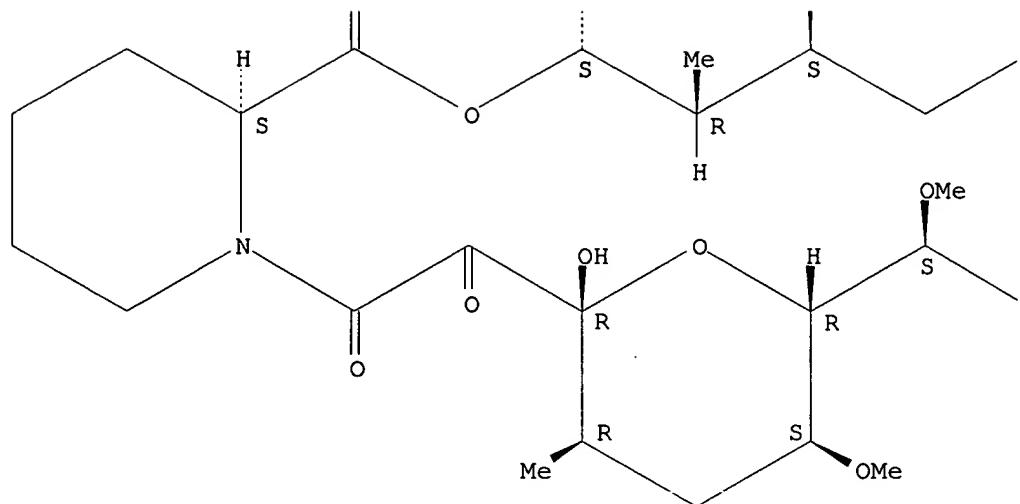
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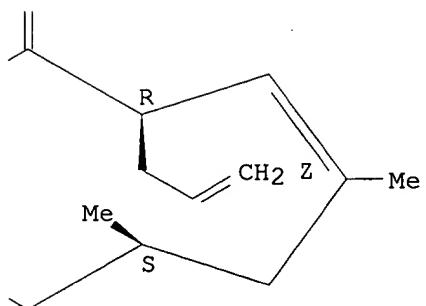
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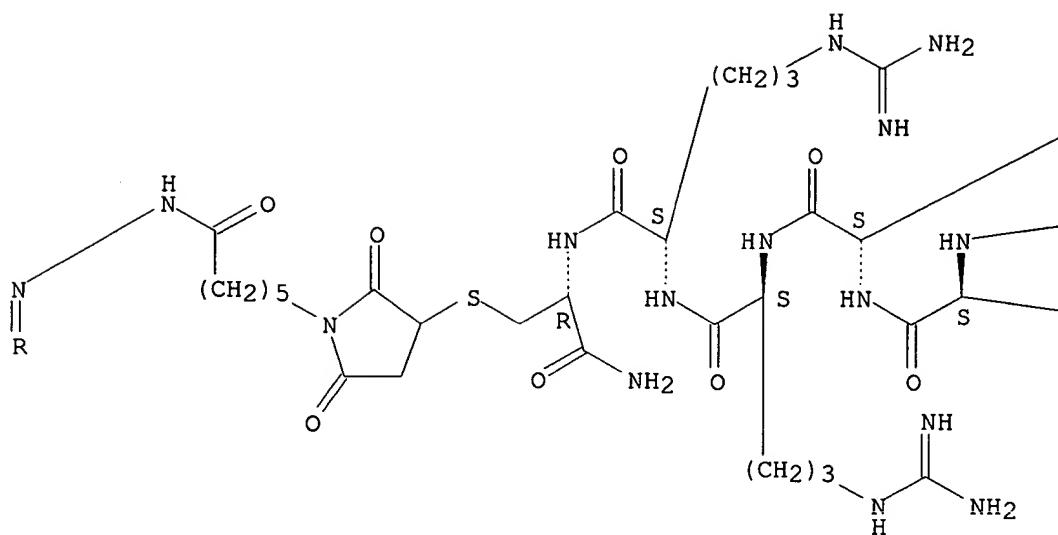
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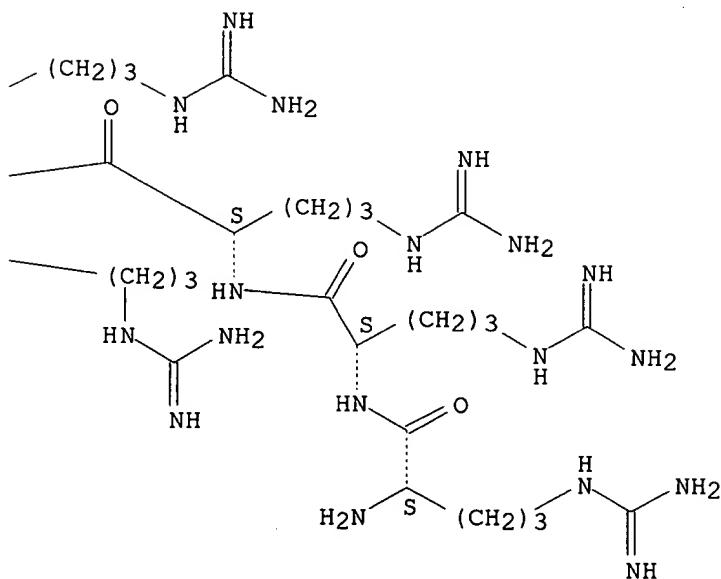
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REFERENCE 1: 137:237728

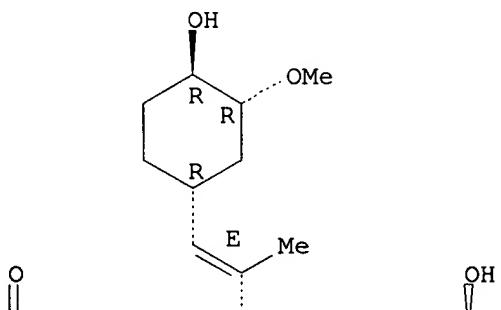
REFERENCE 2: 137:222033

RN 455282-19-6 REGISTRY
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 5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
 methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-
 propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-
 ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX
 NAME)
 FS PROTEIN SEQUENCE; STEREOSEARCH
 MF C99 H174 N34 O22 S
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

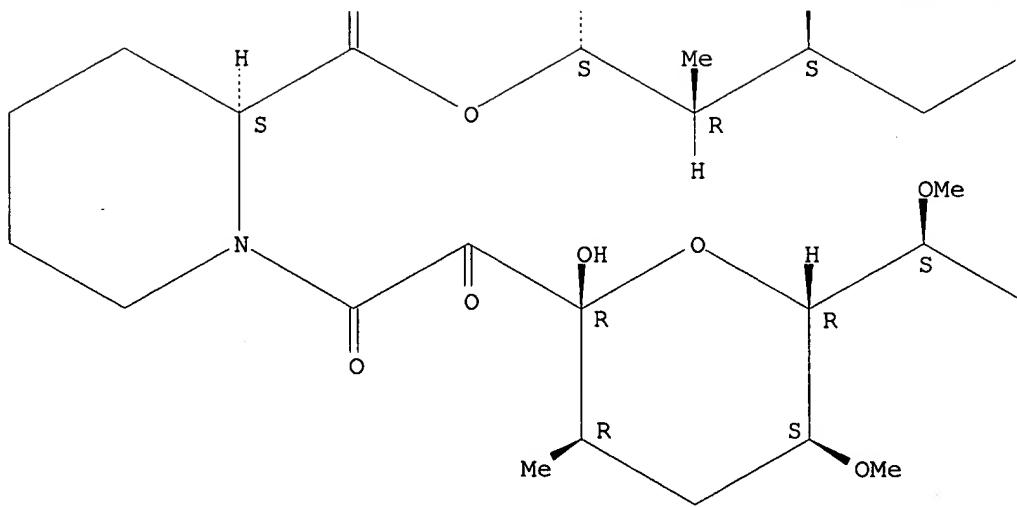
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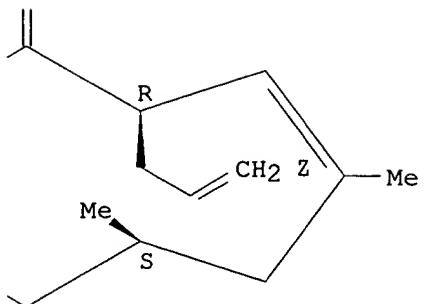
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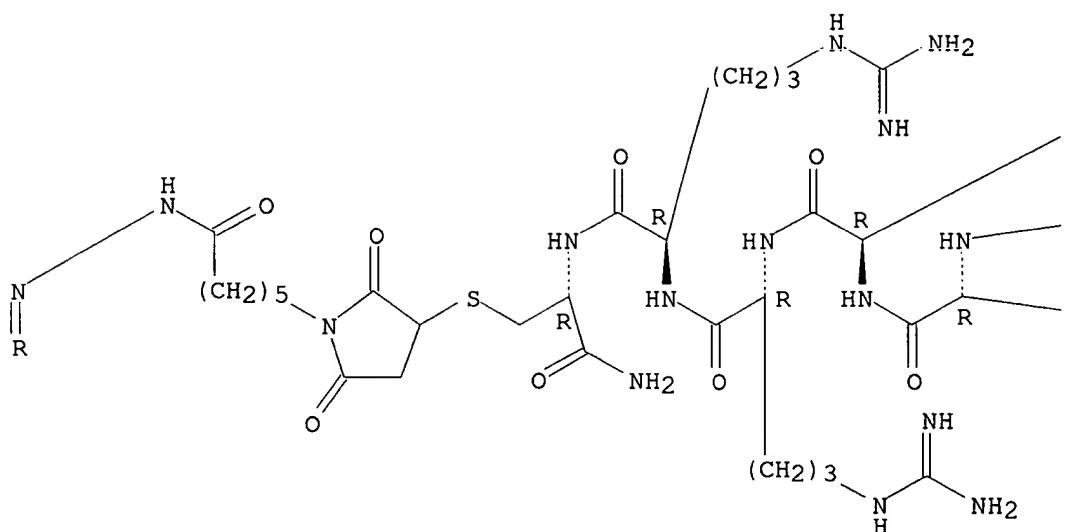
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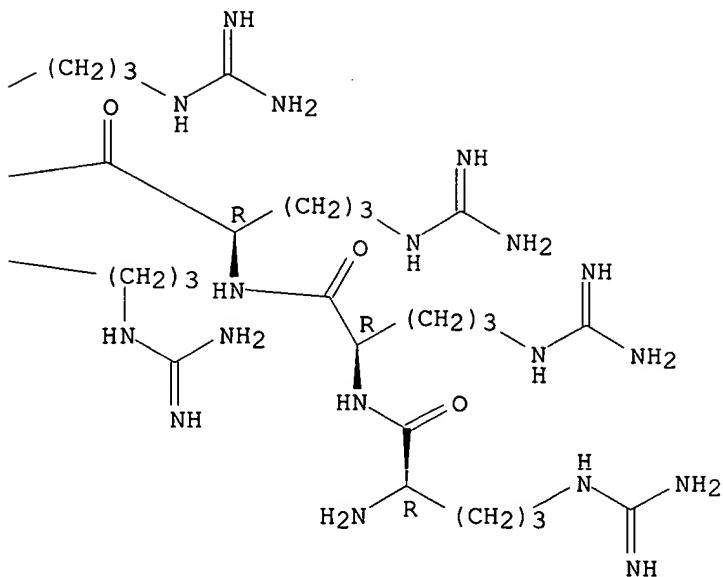


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2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:237728

REFERENCE 2: 137:222033

L16 ANSWER 4 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 455282-18-5 REGISTRY

CN 1-Pyrrolidinehexanoic acid, 3-[(2R)-3-amino-2-[[6-[[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxohexyl]amino]-3-oxopropyl]thio]-2,5-dioxo-, [(3S,4R,5S,8R,9Z,12S,14S,15R,16S,18R,19R,26aS)-1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]hydrazide (9CI) (CA INDEX NAME)

FS STEREOSEARCH

MF C73 H115 N9 O18 S2

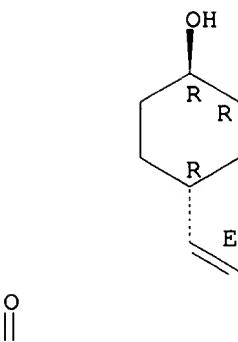
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

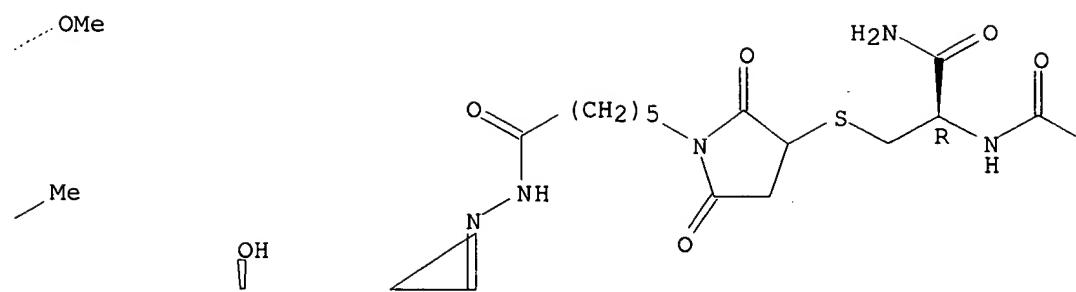
Absolute stereochemistry.

Double bond geometry as described by E or Z.

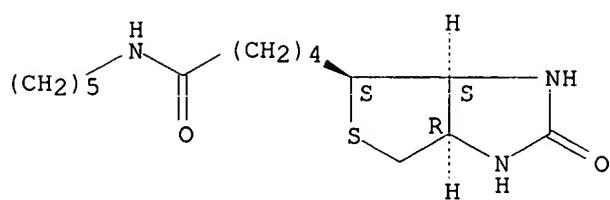
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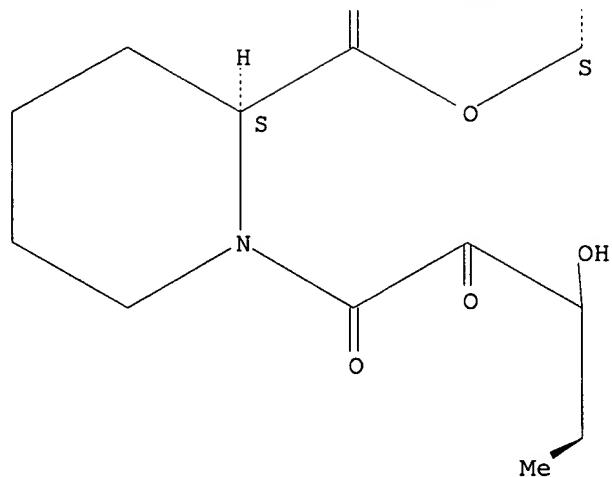
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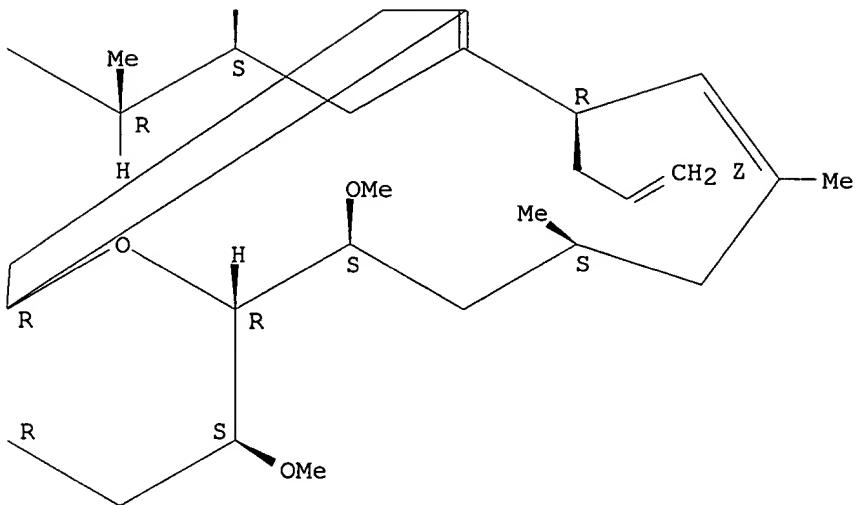
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2 REFERENCES IN FILE CA (1962 TO DATE)
 2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:237728

REFERENCE 2: 137:222033

L16 ANSWER 5 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 455282-17-4 REGISTRY

CN L-Cysteinamide, N2-[6-[(5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxohexyl]-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-S-[1-[(3S,4R,5S,8R,9Z,12S,14S,15R,16S,18R,19R,26aS)-1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C115 H199 N37 O25 S2

SR CA

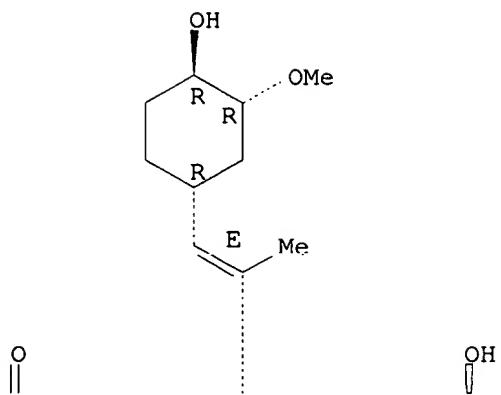
LC STN Files: CA, CAPLUS, USPATFULL

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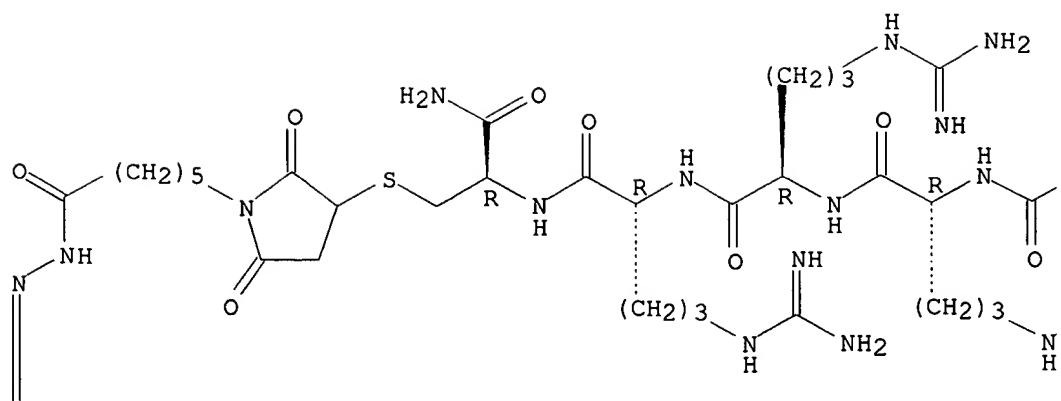
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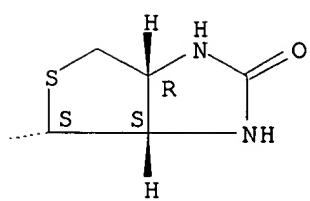
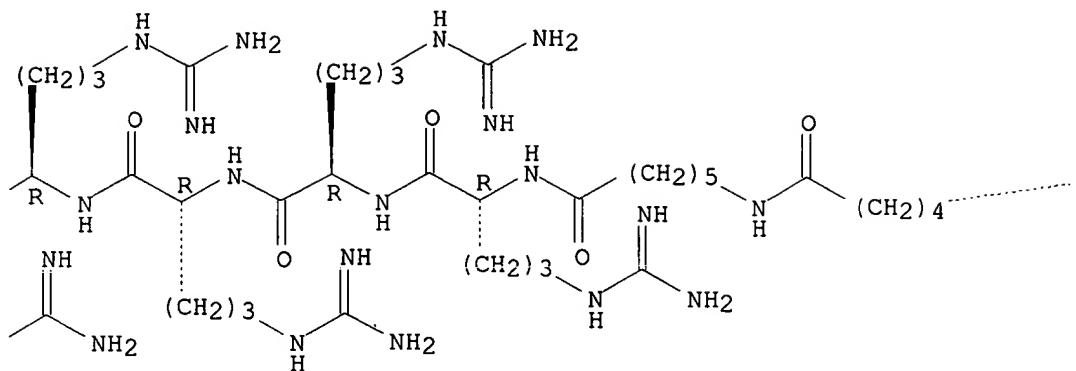
Double bond geometry as described by E or Z.

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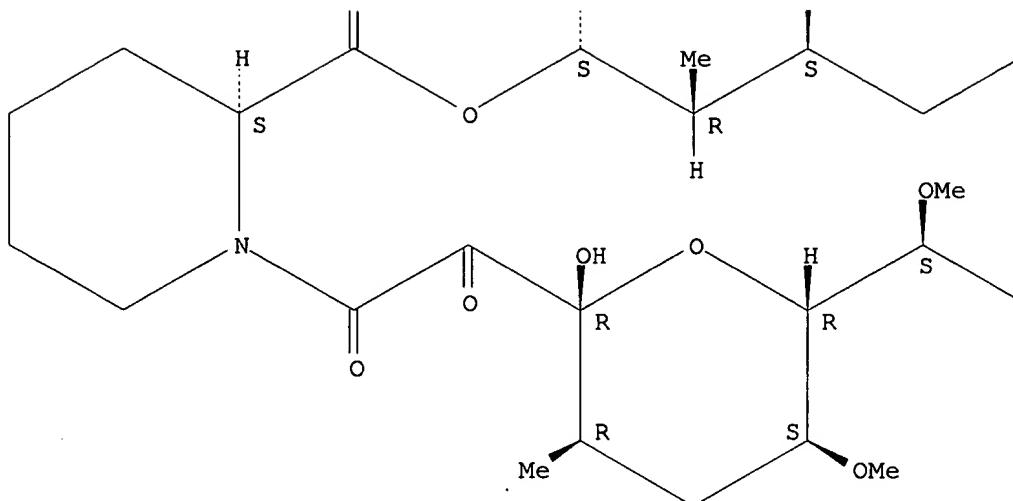


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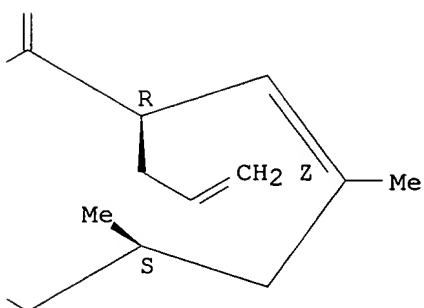




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REFERENCE 1: 137:237728

REFERENCE 2: 137:222033

L16 ANSWER 6 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 455282-16-3 REGISTRY

CN L-Cysteinamide, N2-[6-[(5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]amino]-1-oxohexyl]-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-D-arginyl-S-[1-[6-[(3S,4R,5S,8R,9Z,12S,14S,15R,16S,18R,19R,26aS)-1,3,4,5,6,8,11,12,13,14,15,16,17,18,19,20,21,23,24,25,26,26a-docosahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethethyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-1,20,21-trioxo-8-(2-propenyl)-15,19-epoxy-7H-pyrido[2,1-c][1,4]oxaazacyclotricosin-7-ylidene]hydrazino]-6-oxohexyl]-2,5-dioxo-3-pyrrolidinyl]- (9CI) (CA INDEX NAME)

FS PROTEIN SEQUENCE; STEREOSEARCH

MF C127 H223 N45 O27 S2

SR CA

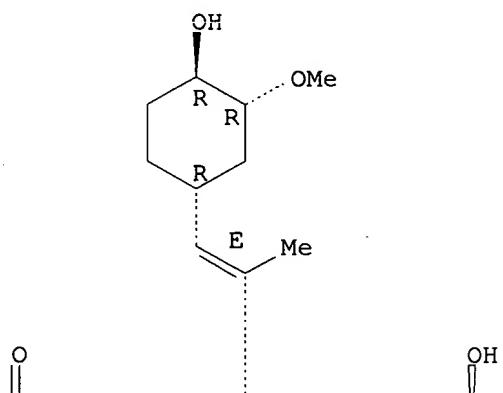
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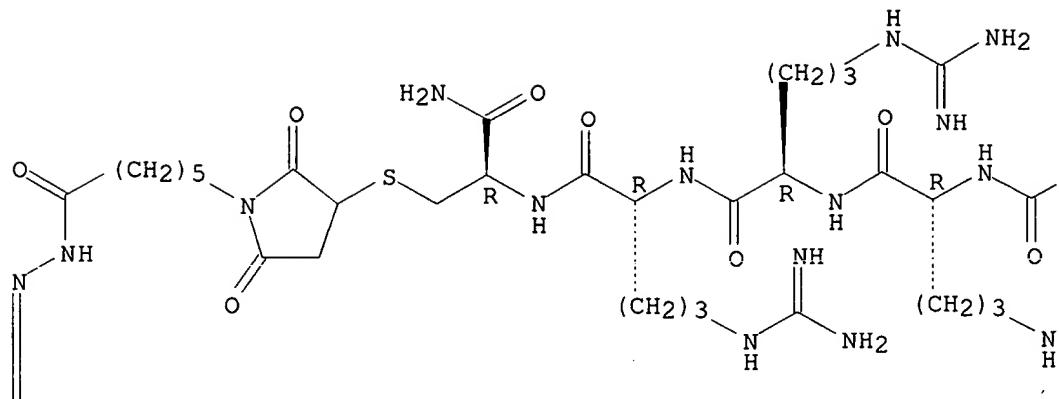
Absolute stereochemistry.

Double bond geometry as described by E or Z.

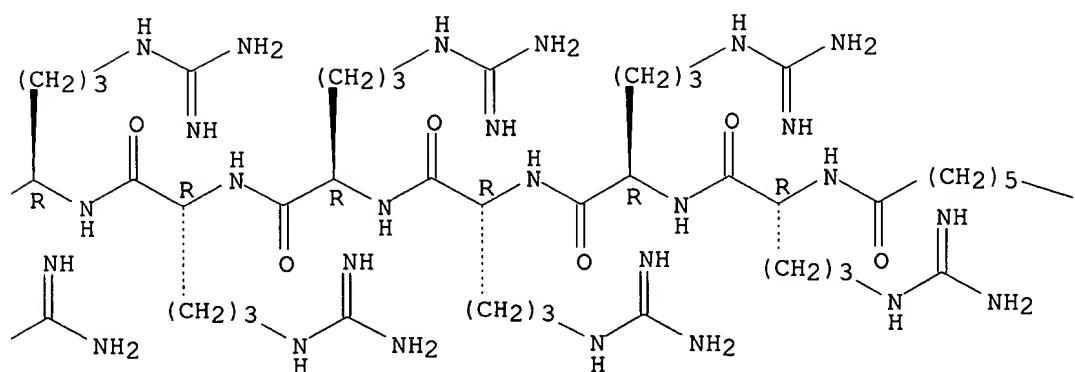
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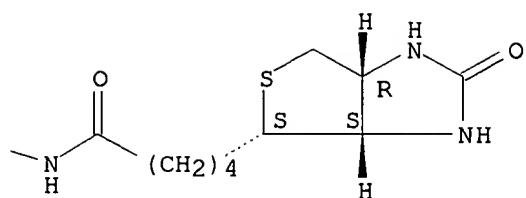
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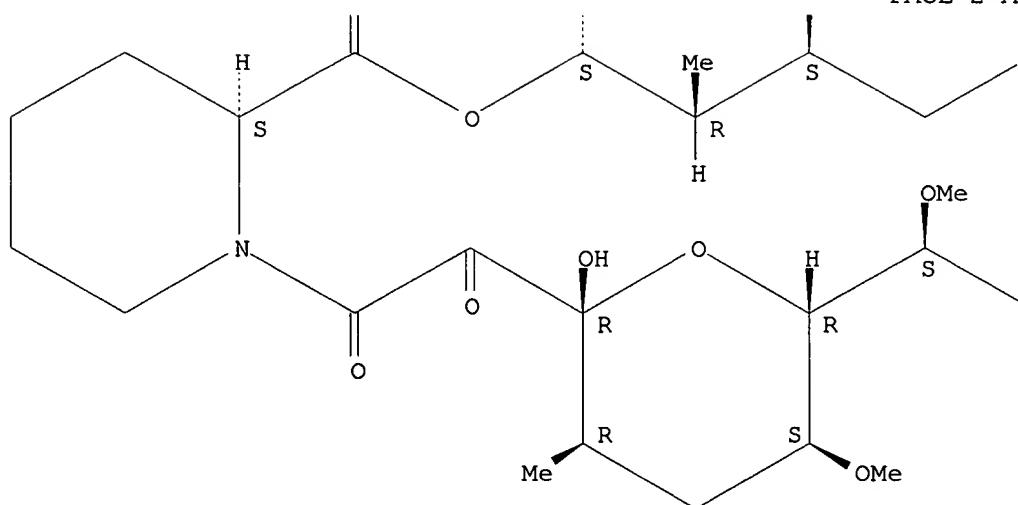
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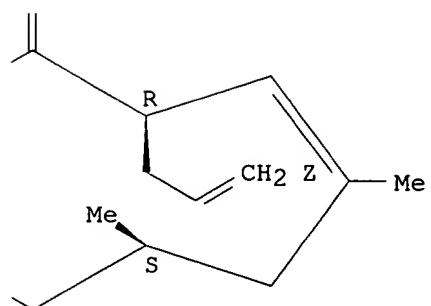
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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:237728

REFERENCE 2: 137:222033

L16 ANSWER 7 OF 8 REGISTRY COPYRIGHT 2003 ACS

RN 104987-12-4 REGISTRY

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

OTHER NAMES:

CN Ascomycin

CN FK 520

CN FR 520

CN FR 900520

CN Immunomycin

CN L 683590

FS STEREOSEARCH

DR 11011-38-4, 159430-76-9, 126340-36-1, 133876-12-7, 136457-58-4, 137767-75-0, 148400-02-6

MF C43 H69 N O12

SR CA

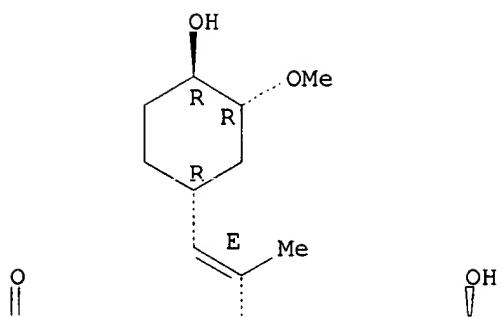
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIUDB, MEDLINE, NAPRALERT, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.

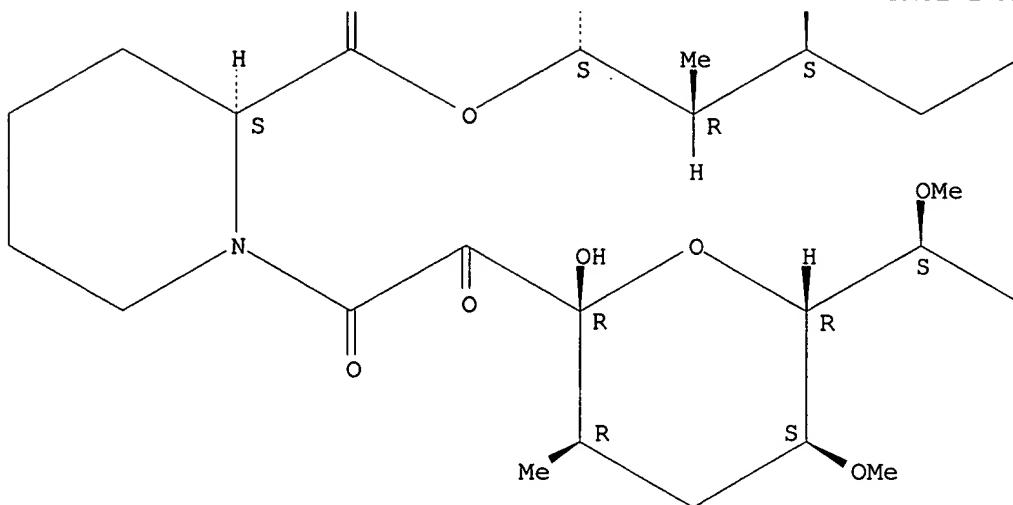
Double bond geometry as described by E or Z.

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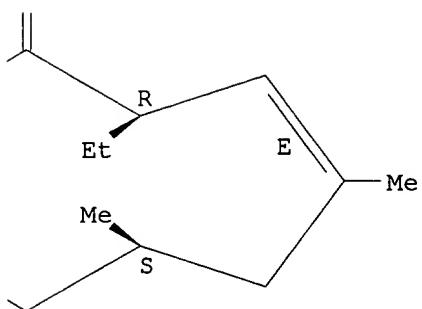


PAGE 1-B

PAGE 2-A



PAGE 2-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

240 REFERENCES IN FILE CA (1962 TO DATE)
 38 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 241 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:66697
 REFERENCE 2: 138:23766
 REFERENCE 3: 138:8377
 REFERENCE 4: 138:8348
 REFERENCE 5: 137:299948
 REFERENCE 6: 137:237728
 REFERENCE 7: 137:218731
 REFERENCE 8: 137:215879

REFERENCE 9: 137:210973

REFERENCE 10: 137:185341

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RN 104987-11-3 REGISTRY

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, [3S-[3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-

OTHER NAMES:

CN (-)-FK 506

CN FK 506

CN FR 900506

CN Fujimycin

CN L 679934

CN Prograf

CN Protopic

CN Tacrolimus

CN Tsukubaenolide

FS STEREOSEARCH

MF C44 H69 N O12

CI COM

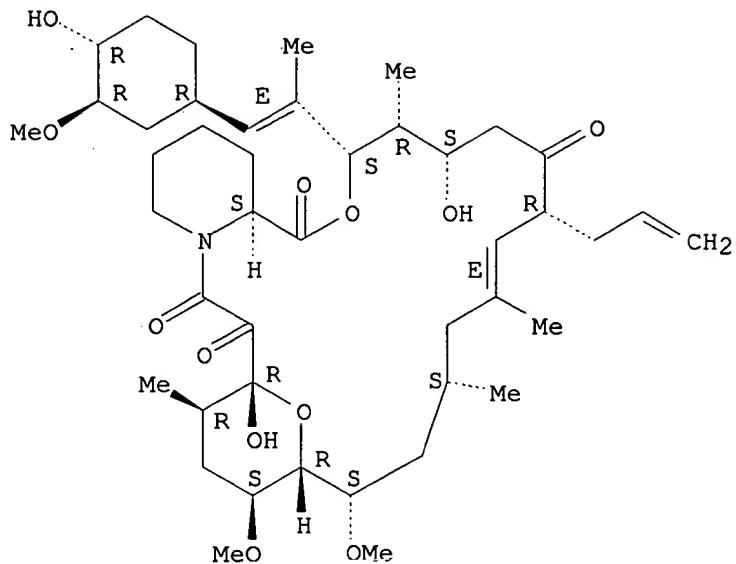
SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPIUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIUDB, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Other Sources: WHO

Absolute stereochemistry.

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3730 REFERENCES IN FILE CA (1962 TO DATE)
 125 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 3747 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:126929
 REFERENCE 2: 138:117567
 REFERENCE 3: 138:117411
 REFERENCE 4: 138:117409
 REFERENCE 5: 138:117405
 REFERENCE 6: 138:112119
 REFERENCE 7: 138:100720
 REFERENCE 8: 138:100501
 REFERENCE 9: 138:95621
 REFERENCE 10: 138:95376